JCS 2018 Guideline on Diagnosis of Chronic Coronary Heart Diseases

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Refer to Appendix I for the details of members.
Joint Working Groups: Japanese Circulation Society, Japan Radiological Society, Japanese Society of Nuclear Medicine, Japanese Society of Medical Imaging, Japanese Society of Cardiovascular Medicine, Japanese Society of Nuclear Cardiology, Japan College of Cardiology, Japan Society of Ultrasonics in Medicine, Japan Atherosclerosis Society, Japanese Heart Rhythm Society, and Japanese College of Angiology.
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Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ABI</td>
<td>ankle–brachial index</td>
</tr>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>APV</td>
<td>averaged peak velocity</td>
</tr>
<tr>
<td>ARH</td>
<td>autosomal recessive hypercholesterolemia</td>
</tr>
<tr>
<td>AS</td>
<td>Agatston score</td>
</tr>
<tr>
<td>ASO</td>
<td>arteriosclerosis obliterans</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>BMIPP</td>
<td>β-methyl-p-iodophenyl-pentadecanoic acid</td>
</tr>
<tr>
<td>BNP</td>
<td>brain natriuretic peptide</td>
</tr>
<tr>
<td>CAGB</td>
<td>coronary artery bypass grafting</td>
</tr>
<tr>
<td>CACS</td>
<td>coronary artery calcium score</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CANM</td>
<td>Canadian Association of Nuclear Medicine</td>
</tr>
<tr>
<td>CanSCMR</td>
<td>Canadian Society of Cardiovascular Magnetic Resonance</td>
</tr>
<tr>
<td>CAR</td>
<td>Canadian Association of Radiologists</td>
</tr>
<tr>
<td>CCS</td>
<td>Canadian Cardiovascular Society</td>
</tr>
<tr>
<td>CCTA</td>
<td>coronary CT angiography</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CFR</td>
<td>coronary flow reserve</td>
</tr>
<tr>
<td>CFVR</td>
<td>coronary flow velocity reserve</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>CNCS</td>
<td>Canadian Nuclear Cardiology Society</td>
</tr>
<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTA</td>
<td>computed tomography angiography</td>
</tr>
<tr>
<td>CTDvol</td>
<td>computed tomography dose index volume</td>
</tr>
<tr>
<td>DES</td>
<td>drug-eluting stent</td>
</tr>
<tr>
<td>DLP</td>
<td>dose–length product</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiography</td>
</tr>
<tr>
<td>EDV</td>
<td>end-diastolic volume</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>ESV</td>
<td>end-systolic volume</td>
</tr>
<tr>
<td>FBP</td>
<td>filtered back projection</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FDG</td>
<td>fluorodeoxyglucose</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>fluorodeoxyglucose–positron emission tomography</td>
</tr>
<tr>
<td>FFR</td>
<td>fractional flow reserve</td>
</tr>
<tr>
<td>FFR-CT</td>
<td>CT-derived fractional flow reserve</td>
</tr>
<tr>
<td>FH</td>
<td>familial hypercholesterolemia</td>
</tr>
<tr>
<td>1/3FR mean</td>
<td>one-third mean filling rate</td>
</tr>
<tr>
<td>GLS</td>
<td>global longitudinal strain</td>
</tr>
<tr>
<td>ICD</td>
<td>implantable cardioverter defibrillator</td>
</tr>
<tr>
<td>iFR</td>
<td>instantaneous wave-free ratio</td>
</tr>
<tr>
<td>IMT</td>
<td>intima–media thickness</td>
</tr>
<tr>
<td>IVUS</td>
<td>intravascular ultrasound</td>
</tr>
<tr>
<td>LDL</td>
<td>low-density lipoprotein</td>
</tr>
<tr>
<td>LGE</td>
<td>late gadolinium enhancement</td>
</tr>
<tr>
<td>LP</td>
<td>late potential</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>MACE</td>
<td>major adverse cardiovascular events</td>
</tr>
<tr>
<td>MDCT</td>
<td>multidetector [row] CT</td>
</tr>
<tr>
<td>MIBI</td>
<td>methoxy-isobutyl isonitrile</td>
</tr>
<tr>
<td>MRA</td>
<td>magnetic resonance angiography</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>M-TWA</td>
<td>microvolt (μV)–T wave alternans</td>
</tr>
<tr>
<td>NSF</td>
<td>nephrogenic systemic fibrosis</td>
</tr>
<tr>
<td>NURD</td>
<td>non-uniform rotational distortion</td>
</tr>
<tr>
<td>OCT</td>
<td>optical coherence tomography</td>
</tr>
<tr>
<td>OM1</td>
<td>old (previous) myocardial infarction</td>
</tr>
<tr>
<td>PAD</td>
<td>peripheral arterial disease</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
</tr>
<tr>
<td>PESP</td>
<td>postextrasystolic potentiation</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PFR</td>
<td>peak filling rate</td>
</tr>
<tr>
<td>QCA</td>
<td>quantitative coronary angiography</td>
</tr>
<tr>
<td>QOL</td>
<td>quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>SAE</td>
<td>signal-averaged ECG</td>
</tr>
<tr>
<td>SPECT</td>
<td>single photon emission computed tomography</td>
</tr>
<tr>
<td>Tc</td>
<td>technetium</td>
</tr>
<tr>
<td>TBI</td>
<td>toe–brachial index</td>
</tr>
<tr>
<td>TOF</td>
<td>time-of-flight</td>
</tr>
<tr>
<td>TPF</td>
<td>time-to-peak filling</td>
</tr>
<tr>
<td>TWA</td>
<td>T-wave alternans</td>
</tr>
</tbody>
</table>
There have been remarkable advances in the methods used for diagnosis and clinical evaluation of cardiovascular diseases. Noninvasive diagnostic techniques have developed to unprecedented levels over the past decade, particularly those using CT, MRI, radioisotope (RI) imaging, and echocardiography. Intravascular imaging was initiated as IVUS, and there has been significant progress in the field of functional evaluation as well as morphological evaluation.

The first edition of this Guideline was released in 1998–99 to provide an overview of the wide variety of examinations available for coronary heart diseases and the status of each examination at that time. The Guideline was subsequently revised in 2005 and 2010 as Guidelines for Diagnostic Evaluation of Patients with Chronic Ischemic Heart Diseases to incorporate new advances in testing. In addition to this area, the Guideline has undergone substantial revision based on the JCS 2010 Guidelines for Clinical Use of Cardiac Nuclear Medicine\(^1\) and the JCS 2009 Guidelines for Noninvasive Diagnosis of Coronary Artery Lesions.\(^2\)

This revised version has 3 parts, which cover the information provided in the first version and the previous revised versions, as well as risk assessment. Chapter I covers the “Significance of Various Tests for Diagnosis of Chronic Coronary Heart Disease”, and describes the characteristics and technical aspects of each test, as well as the conditions for which each test is useful. Chapter II – “Risk Assessment and Management” – has been newly added in this version. Chapter III, “Selecting Tests for Chronic Coronary Heart Disease Based on the Pathological Condition and Diagnostic Objectives”, explains how to select and use various test methods for evaluating disease states, the prognosis, and the effects of treatment. References to the literature published since 2010 have been added during the preparation of this Guideline. Data obtained in Japan were reviewed whenever possible. Some information about acute myocardial infarction and unstable angina has been excluded because separate guidelines are available for these conditions.

This Guideline is designed to assist clinicians, especially cardiologists, diagnose chronic coronary heart disease, evaluate its severity, formulate a treatment plan, assess the response to treatment, and manage patients. In particular, the characteristics and diagnostic performance of each test are explained, as well as how effective each test is for different diagnostic purposes and disease states, together with the potential pitfalls. In addition, this Guideline is intended to provide support for selecting a combination of multiple tests so that the information required to treat individual patients can be obtained. For this reason, the “Level of evidence”, which indicates the relationship between each test/diagnosis and clinical outcomes, is also mentioned whenever possible, although it can be difficult to establish evidence for such relationships. Accordingly, this Guideline may also be useful for other healthcare professionals in addition to clinicians. We hope this Guideline will be a source of useful information in hospitals, outpatient clinics, and laboratories.

### Recommendations and Levels of Evidence

In this Guideline, the recommendations and levels of evidence are classified in accordance with recent guidelines of the Japanese Circulation Society, the ACC/AHA, and the ESC (Tables 1, 2). These guidelines are already widely used, so adopting the same classification facilitates comparison between Japanese and overseas guidelines.

In Japan, the recommendation grades and levels of evidence proposed by the Medical Information Network Distribution Service (MINDS), a medical information service of the Japan Council for Quality Health Care, have recently been widely adopted (Tables 3, 4).\(^3\) The MINDS Guide for Developing Clinical Practice Guidelines 2007\(^3\) provides a classification framework that is slightly different from the conventional recommendation grades/levels of evidence, with the MINDS classification being more oriented towards tests and research.

Because these classifications are useful, both are included in this Guideline whenever possible. The recommendations presented herein were first determined by the individual authors based on the literature published in Japan and overseas, and then were assessed by peer review in meetings of Study Group members and the External Evaluation Committee.

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Evidence and/or general agreement that a given procedure or treatment is useful and effective</td>
</tr>
<tr>
<td>Class II</td>
<td>Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given procedure or treatment</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Weight of evidence/opinion is in favor of usefulness/efficacy</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence/opinion</td>
</tr>
<tr>
<td>Class III</td>
<td>Evidence or general agreement that the given procedure or treatment is not useful/effective, and in some cases may be harmful</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level A</td>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
</tr>
<tr>
<td>Level B</td>
<td>Data derived from a single randomized clinical trial or large-scale nonrandomized studies</td>
</tr>
<tr>
<td>Level C</td>
<td>Consensus of opinion of the experts and/or small-size clinical studies, retrospective studies, and registries</td>
</tr>
</tbody>
</table>
Pretest Probability and Cardiovascular Risk

This Guideline describes and provides guidance on the Significance of Various Tests for Diagnosis of Chronic Coronary Heart Disease, Risk Assessment and Management, and Selecting Tests for Chronic Coronary Heart Disease Based on the Pathological Condition and Diagnostic Objectives. The pretest probability for each test is listed as low (<30%), medium (≥30 and <70%), or high (≥70%).

Cardiovascular risk is described in accordance with the classification in the Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017 from the Japan Atherosclerosis Society, which defines the expected risk of developing coronary heart disease in a 10-year period as low (<2%), medium (2% and <9%), or high (≥9%).

However, because some of the literature classifies those risks by different criteria, separate descriptions are provided in such cases.

I. Significance of Various Tests for Diagnosis of Chronic Coronary Heart Disease

1. Exercise Electrocardiography

The most important purpose of exercise ECG is to diagnose coronary heart disease. Electrocardiography assesses the electrical activity of the myocardium and thus reflects myocardial ischemia, so whether exercise produces ischemic changes on the electrocardiogram is investigated. Determining myocardial ischemia indicates the presence of functional coronary stenosis. Accordingly, exercise ECG is complementary to coronary angiography, which provides a morphological evaluation of coronary artery stenosis. In addition to diagnosing coronary heart disease, ECG is also used for follow-up after coronary revascularization, preoperative examination before noncardiac surgery in patients with coronary heart disease, cardiac rehabilitation, and prescription of exercise for lifestyle-related diseases. In the USA and Europe, the Duke treadmill score is used to predict the long-term prognosis.6 5

1.1 Sensitivity and Specificity

The sensitivity and specificity of exercise ECG for detecting coronary artery stenosis are approximately 75% and 70%, respectively,6 4 and the pretest probability for an individual patient should also be taken into consideration.6 Pretest probability is related to the percentage of persons with the target disease in a particular population. In populations with a high prevalence of coronary heart disease, such as older men with multiple coronary risk factors and typical angina pain, the probability of coronary heart disease existing (a true-positive result) is very high if exercise ECG is positive. Moreover, even if ECG is negative, there is the possibility of a false-negative result. Conversely, even if exercise ECG is positive in persons from a young or middle-aged population, they often have normal coronary arteries (a false-positive result). Clinicians should decide on the next diagnostic step by comprehensive evaluation, together with assessment of whether exercise ECG is positive or negative.

1.2 Indications and Contraindications

In addition to making a definitive diagnosis of suspected coronary heart disease, exercise ECG can be used for screening high-risk patients and for follow-up of patients with coronary heart disease after coronary revascularization or during drug therapy. Each of these uses will be detailed in the itemized discussion.

Contraindications to this test include acute myocardial
infarction and severe valvular disease, because exercise aggravates these conditions (Table 5). The AHA guideline states that exercise ECG can be performed in patients with suspected unstable angina, providing that the risk is deemed to be low based on pretest evaluation. In patients with secondary ST changes, such as Wolff-Parkinson-White syndrome (WPW syndrome) or left bundle branch block, the diagnosis of coronary heart disease cannot be made by ECG alone, and combining an imaging test such as exercise myocardial scintigraphy with exercise echocardiography may be useful.

### 1.3 Safety and Points to Check

Exercise ECG is generally safe, however, because it is a stress test, it must be assumed that myocardial ischemia could be induced and may lead to a cardiac event. Accordingly, prior to performing this test it must be explained to the patient that there is a certain risk of myocardial infarction or even sudden death. It is also necessary to obtain a signed consent form. In addition, an emergency cart with a defibrillator, drugs, infusion sets, and intubation tubes should be available in the laboratory in case an emergency occurs, and the quickest route to the emergency department should be identified.

### 1.4 Protocols

Exercise ECG methods include the classical Master two-step test, the treadmill test, and the bicycle ergometer test. The Master test can be single (1.5 min), double (3 min), or triple (4.5 min). Because the Master test is relatively simple and does not require a special device for exercise, it has been widely used in the present time. However, it is preferable to use the treadmill or ergometer method because the exercise load cannot be controlled during the Master test. Accordingly, exercise tolerance cannot be evaluated with the Master test, although it is an important prognostic indicator, and electrocardiographic changes cannot be captured during exercise. Particularly, this test should not be performed in high-risk patients.

As for the treadmill test, the Bruce protocol is a widely used standard for increasing the speed and inclination of the treadmill (Table 6). The duration of the light exercise

---

**Table 5. Contraindications of Exercise Stress Testing**

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>① Acute myocardial infarction, unstable angina</td>
</tr>
<tr>
<td>② Uncontrolled arrhythmia</td>
</tr>
<tr>
<td>③ Symptomatic severe aortic valve stenosis</td>
</tr>
<tr>
<td>④ Acute or severe heart failure</td>
</tr>
<tr>
<td>⑤ Acute pulmonary embolism or lung infarction</td>
</tr>
<tr>
<td>⑥ Acute myocarditis or pericarditis</td>
</tr>
<tr>
<td>⑦ Aortic dissection or aneurysm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>① Left main stenosis</td>
</tr>
<tr>
<td>② Moderate aortic valve stenosis</td>
</tr>
<tr>
<td>③ Severe electrolytic abnormality</td>
</tr>
<tr>
<td>④ Severe hypertension</td>
</tr>
<tr>
<td>⑤ Tachyarrhythmia or bradyarrhythmia</td>
</tr>
<tr>
<td>⑥ Obstructive hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>⑦ Mental and physical disturbance which cannot exercise</td>
</tr>
<tr>
<td>⑧ Advanced atrioventricular block</td>
</tr>
</tbody>
</table>

(Reproduced from Bruce et al 1963, with permission.)

**Table 6. Bruce Protocol**

<table>
<thead>
<tr>
<th>Stage (each 3 min)</th>
<th>Speed mile/h (km/h)</th>
<th>Slope (%)</th>
<th>Estimate METs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.7 (2.7)</td>
<td>10</td>
<td>4.8</td>
</tr>
<tr>
<td>2</td>
<td>2.5 (4.0)</td>
<td>12</td>
<td>6.8</td>
</tr>
<tr>
<td>3</td>
<td>3.4 (5.5)</td>
<td>14</td>
<td>9.6</td>
</tr>
<tr>
<td>4</td>
<td>4.2 (6.9)</td>
<td>16</td>
<td>13.2</td>
</tr>
<tr>
<td>5</td>
<td>5.0 (8.0)</td>
<td>18</td>
<td>16.6</td>
</tr>
<tr>
<td>6</td>
<td>5.5 (8.8)</td>
<td>20</td>
<td>20.0</td>
</tr>
<tr>
<td>7</td>
<td>6.0 (9.6)</td>
<td>22</td>
<td>–</td>
</tr>
</tbody>
</table>

(Reproduced from Bruce et al 1963, with permission.)

---

The test should be conducted under the supervision of a highly experienced doctor and several ancillary staff, including laboratory technicians and nurses, with the symptoms, ECG, heart rate, and blood pressure being monitored. In addition to assessing electrocardiographic changes at the onset of symptoms, great care should be taken to not overlook asymptomatic ischemic changes, arrhythmias, or changes in blood pressure.
Table 8. Criteria for Ischemia on Exercise Stress ECG

<table>
<thead>
<tr>
<th>Definite criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST depression</td>
</tr>
<tr>
<td>&gt;0.1mV horizontal, downsloping (measure 0.06–0.08 s after J point)</td>
</tr>
<tr>
<td>ST elevation</td>
</tr>
<tr>
<td>&gt;0.1mV</td>
</tr>
<tr>
<td>ST depression at rest</td>
</tr>
<tr>
<td>&gt;0.2mV horizontal, downsloping</td>
</tr>
</tbody>
</table>

Reference finding

<table>
<thead>
<tr>
<th>Findings suggesting false positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance of negative U wave in the precordial leads</td>
</tr>
<tr>
<td>HR-ST loop rotates counterclockwise</td>
</tr>
<tr>
<td>When upsloping ST depression during exercise gradually changes to horizontal or downsloping after exercise and continues for a long time (late recovery pattern)</td>
</tr>
<tr>
<td>ST changes associated with left ventricular hypertrophy</td>
</tr>
<tr>
<td>Early recovery from ST change</td>
</tr>
</tbody>
</table>

(stage may be shortened in subjects with a high exercise capacity, based on the interview conducted before examination. On the other hand, the initial load may be increased more slowly in subjects with a low exercise capacity, patients with a low angina pain threshold, and elderly persons. In principle, the symptom-limited load should be applied with reference to the criteria for stopping exercise (Table 7).

Findings suggesting false positive

- Appearance of negative U wave in the precordial leads
- HR-ST loop rotates counterclockwise
- When upsloping ST depression during exercise gradually changes to horizontal or downsloping after exercise and continues for a long time (late recovery pattern)
- ST changes associated with left ventricular hypertrophy
- Early recovery from ST change

Table 9. Recommendations and Levels of Evidence for Exercise ECG

<table>
<thead>
<tr>
<th>Diagnostic purpose of chronic coronary heart diseases</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I B C1 IVb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

1.5 Indices for Evaluation

1.5.1 ST Depression

In the double Master test, ST depression of 0.1 mV has been reported to show a sensitivity of 77% and specificity of 83% for detecting ≥75% coronary artery stenosis. In Japan, horizontal or sagging ST depression of ≥0.1 mV is the most common criterion for a positive test.

When the treadmill test is performed, the most common criterion for myocardial ischemia is the extent of ST-segment depression from baseline (PQ junction) at 0.06–0.08 s after the J point (Table 8). The test is judged to be positive when depression of ≥0.1 mV occurs and the ST segment is horizontal or sagging. If ST depression is present on resting ECG, a further decrease of 0.2 mV from the resting level is the criterion for a positive result. An upsloping ST segment that shows depression during exercise, gradually changes to horizontal or sagging after the finish of exercise, and then persists for a long time with T-wave inversion suggests a false-positive result.

In patients with coronary heart disease, it is known that ST depression occurs more frequently as more coronary branches are affected by stenosis. ST depression of ≥0.2 mV, ST depression that occurs with light exercise, a poor blood pressure response to exercise, and low exercise tolerance are indicators of an adverse prognosis. Even if ST depression is significant, a small ST/HR slope raises the possibility of a false-positive result. In addition, if the ST/HR slope shows counterclockwise rotation, the probability of a false-positive result is high.

ST elevation is assessed by measurement from the pre-exercise ST level. ST elevation in leads except V1 suggests transmural ischemia. In patients with a history of myocardial infarction, ST elevation with an abnormal Q wave may be caused by abnormal wall motion or reciprocal changes due to ischemia in other regions in addition to ischemia of the infarcted myocardium.

1.5.2 Other Findings

A negative U wave in the anterior precordial leads suggests myocardial ischemia. Because the baseline shifts during exercise, it is difficult to correctly evaluate; it is necessary to observe the baseline with the patient in a stable condition immediately after the end of exercise. Detection of a negative U wave is not sensitive, but shows high specificity, and has been reported to indicate central involvement of the left anterior descending artery and to be an indicator of a poor prognosis. It has also been reported that a positive U wave in the right chest leads during exercise reflects posterior inferior wall ischemia and suggests a lesion in the left circumflex artery or the right coronary artery. Although it has been reported that the R wave height and the Q wave depth are useful for diagnosis of coronary heart disease, the specificity of such findings is considered not to be high.

In patients with bundle branch block, WPW syndrome, or using digitalis, ST depression is not a criterion for diagnosis of coronary heart disease.

1.6 Future Challenges

Exercise ECG is the most common test performed for patients with chest pain, but the chief problem is that its sensitivity and specificity are not necessarily high. According to a meta-analysis of 24,074 subjects, diagnosis of coronary heart disease based on ST depression of 0.1 mV showed a
sensitivity of 68% and specificity of 77%. Similarly, Japanese reports covering 1,055 subjects indicated that the sensitivity and specificity of this criterion were 73% and 74%, respectively. Additional information should be obtained in high-risk patients with negative exercise ECG, low-risk patients with positive exercise ECG, and patients who show abnormal Q waves or ST changes on resting ECG (Table 9).

2. Holter Electrocardiography

2.1 Characteristics and Technical Aspects

Holter ECG is a method of ambulatory monitoring that is characterized by recording for an extended period (24–48 hours), while allowing the subject the freedom to participate in normal daily life. However, it may be difficult to respond to the occurrence of a hazardous electrocardiographic change because analysis is performed after recording has been completed. Moreover, Holter ECG often provides a limited amount of information because of the small number of leads (usually 2–3), although 12-lead Holter ECG has become available in recent years.

In addition to typical Holter ECG, other ambulatory ECG examinations include wireless 1- or 2-lead Holter ECG, extracorporeal or implantable event-switched loop recording, and portable ECG. These methods have value in the diagnosis of arrhythmias and syncopal attacks.

The disposable electrode that is used remains electrically and mechanically stable for a long time. The recorder is compact and lightweight for portability, is robust, and remains electrically and mechanically stable for an extended period. A digital card or IC memory recorder is used for recording information. The speed and accuracy of analysis have been improved thanks to recent remarkable developments in computers. However, the accuracy of the time base, the false-positive and false-negative rates of waveform analysis, and the reproducibility of results vary among manufacturers.

2.2 Points to Consider

2.2.1 Selection of the Lead System and Recording Time

Appropriate ECG recording is essential for making a diagnosis of coronary heart disease. Care should be exercised with regard to selection of the electrodes, leads, paste, and lead system to obtain stable recordings during daily activities. The leads that are most likely to reflect ischemic changes are V5-like leads. In particular, lead CM5 is less affected by body movements and has a good detection rate for ischemic changes. A 2-lead system is commonly used, and the AHA guidelines recommend a combination of leads that approximates leads V1 and V5. For capturing ST elevation in patients with variant angina, vertical leads (II, III, and aVF) and approximations to lead V2 or V3 provide a high diagnostic rate. Both circadian and diurnal (day-to-day) variations may exist in relation to the incidence and duration of myocardial ischemia and the extent of ST changes. However, it is difficult to evaluate the influence of diurnal variation based on 24-hour recording, which means that 48-hour recording is desirable for detecting myocardial ischemia and determining the response to treatment.

2.2.2 Criteria for ST-Segment Changes

The diagnostic significance of persistent ST depression on Holter ECG is not high. Rather, detection and evaluation of transient ST-segment changes is more important. The criteria for ST depression are as follows: (1) horizontal or sagging depression of the ST segment by ≥0.1 mV; (2) reaching maximum ST depression after 1 min; and (3) ST depression of ≥0.1 mV lasting for ≥30–60 s compared with the baseline in a controlled state. ST depression is measured at 0.08 s after the S or J point, and J-type ST depression is not judged to be ischemic ST depression. When counting the number of ischemic episodes, the definition adopted is that each ischemic interval should last for at least 1 min. The criterion for ST elevation is elevation of the ST segment by ≥0.1 mV lasting for ≥30–60 s in leads without Q waves. In patients with chest pain and normal resting electrocardiographic findings, research on Holter ECG, treadmill exercise ECG, and coronary angiography has shown that the sensitivity and specificity of Holter ECG for diagnosis of coronary lesions is 62% and 61%, respectively, being lower than the sensitivity and specificity of treadmill exercise ECG (67% and 75%, respectively).

2.2.3 Factors Influencing Assessment of ST-Segment Changes

When evaluating ischemic ST changes on Holter ECG, it is important to discriminate nonischemic ST changes associated with postural changes. ECG should be recorded in advance in the supine, lateral, or standing position, or during hyperventilation, and then used as a reference. Ischemic ST-segment changes occur gradually with an increasing heart rate and it often requires 1 min or longer for the maximum change to develop. The ST-segment trend shows a wedge-shaped change when the cause is ischemia. On the other hand, postural ST changes occur rapidly (in several beats to several seconds) together with baseline fluctuation due to the change of posture, and the ST segment trend shows a box-shaped change.

A variety of factors can influence assessment of ST depression. Digitalis can give rise to ST depression with a “sagging” morphology. Some antiarrhythmic drugs, antidepressants, and sedatives cause ST-T changes caused by alterations in repolarization. Hypokalemia and hypopnea may also induce ST changes. ST-T changes caused by repolarization abnormalities associated with left ventricular hypertrophy, intraventricular conduction defects, or preexcitation syndromes (WPW syndrome, etc.) can be difficult to distinguish from ST-segment changes associated with myocardial ischemia. However, evaluation of ST-segment changes in the left chest’s lead is possible in patients with right bundle branch block. Nonspecific ST depression in patients with atrial fibrillation, atrial flutter, and tachyarrhythmias can also lead to false-positive results. In women, horizontal ST depression is often noted even if there are no coronary artery lesions. Thus, the diagnostic accuracy of Holter ECG for myocardial ischemia is low when nonspecific electrocardiographic changes occur because of factors influencing the assessment of ST depression, and in such cases cardiac radionuclide imaging and CCTA are recommended instead.

2.3 Significance in the Diagnosis of Chronic Coronary Heart Disease

In patients with chronic coronary heart disease, the suitable conditions for Holter ECG include vasospastic angina, effort angina with significant coronary artery stenosis, and
asymptomatic myocardial ischemia. Holter ECG is more useful than exercise ECG because it can be used to assess myocardial ischemia during daily activities and for preoperative risk assessment in patients who cannot perform exercise because of physical disability, peripheral vascular disease, or severe pulmonary disease. In addition, 12-lead Holter ECG may be performed to improve the diagnosis of myocardial ischemia, especially asymptomatic myocardial ischemia or transient ischemic events.

Analysis of ST-T changes on the 12-lead recording may allow localization of the sites of myocardial ischemia, even silent or transient ones, and has been reported to be more useful than conventional 2-lead Holter ECG, particularly for detecting ischemia of the posteriorinferior wall. 12-lead Holter ECG is also useful for detecting arrhythmias and identifying the site of origin, as well as for confirming the pacing status after cardiac resynchronization therapy in patients with heart failure. The guidelines proposed by the Japanese Circulation Society and the AHA regarding the indications for Holter ECG in patients with coronary heart disease and vasospastic angina are summarized in Table 10.

### 2.3.1 Asymptomatic Coronary Heart Disease

Asymptomatic myocardial ischemia is defined as objective evidence of myocardial ischemia in patients without symptoms of ischemia. It is common in the elderly and in patients with diabetes. A diagnosis of asymptomatic myocardial ischemia is made by integrating the findings of Holter ECG, exercise testing, and stress myocardial scintigraphy.

Cohn classified asymptomatic myocardial ischemia into 3 types (Table 11). The prevalence of transient myocardial ischemia in apparently healthy adults, corresponding to Cohn’s type I, has been reported to be 1.2–6% in Western countries based on the results of exercise testing. On the other hand, the false-positive rate for ischemic ST depression on Holter ECG is 2–30% (mean: 10.3%) in healthy individuals, and it is extremely difficult to identify transient asymptomatic ischemic ST changes in apparently healthy individuals by this method. In individuals with Cohn’s type II or III asymptomatic ischemia, the detection rate by Holter ECG is 22–59% (mean: 35%) in Western countries. Similar results have also been reported in Japan with Holter ECG being more useful in these groups compared with patients with Cohn’s type I asymptomatic ischemia. When angina pectoris is stratified by the pattern of angina attacks, a closer relationship with coronary tonus is associated with a higher frequency of angina pectoris.

It has been reported that asymptomatic myocardial ischemia is associated with cardiovascular events in patients with diabetes mellitus. When Holter ECG was performed in patients with type 2 diabetes mellitus or impaired glucose tolerance who had no cardiac symptoms despite a 20-year or longer history of diabetes mellitus and risk factors for arteriosclerosis, those showing moderate to severe ischemic ST-T changes and arrhythmias had a high rate of coronary heart disease, and they also had a significantly higher cumulative incidence of future cardiovascular events. On the other hand, it has been reported that routine screening for myocardial ischemia is not recommended in asymptomatic patients with type 2 diabetes mellitus and normal electrocardiographic findings. No conclusion has yet been reached regarding the balance between the benefits, costs, and risks of testing for myocardial ischemia in asymptomatic patients.

### Table 10. Recommendations and Levels of Evidence for Indications for Holter ECG for Ischemia Monitoring for the Diagnosis of Chronic Coronary Heart Disease

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with strongly suspected variant angina, who show unexplained syncope and palpitation</td>
<td>I</td>
<td>C</td>
<td>B</td>
<td>IVb</td>
</tr>
<tr>
<td>Patients with suspected variant angina</td>
<td>IIA</td>
<td>C</td>
<td>B</td>
<td>IVb</td>
</tr>
<tr>
<td>Preoperative evaluation for vascular surgery of patients who cannot exercise</td>
<td>IIA</td>
<td>C</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>Evaluation of patients with chest pain who cannot exercise</td>
<td>IIA</td>
<td>C</td>
<td>C1</td>
<td>VI</td>
</tr>
<tr>
<td>Asymptomatic patients aged over 20 years with type 2 diabetes mellitus or impaired glucose tolerance who have no history of organic heart disease but who do have ≥1 coronary risk factors</td>
<td>IIB</td>
<td>C</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>Patients with known coronary artery disease and atypical chest pain syndrome</td>
<td>IIB</td>
<td>C</td>
<td>C1</td>
<td>VI</td>
</tr>
<tr>
<td>Initial evaluation of patients with chest pain who are able to exercise</td>
<td>III</td>
<td>C</td>
<td>C2</td>
<td>VI</td>
</tr>
<tr>
<td>Routine screening of asymptomatic subjects</td>
<td>III</td>
<td>C</td>
<td>C2</td>
<td>VI</td>
</tr>
</tbody>
</table>

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence. (Reproduced from Crawford et al 1999, Japanese Circulation Society, 2013, and Nakao et al 2015 with permission.)

### Table 11. Classification of Silent Myocardial Ischemia

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Totally asymptomatic</td>
</tr>
<tr>
<td>II</td>
<td>Myocardial infarction but now totally asymptomatic</td>
</tr>
<tr>
<td>III</td>
<td>Angina present, but for each anginal episode ≥1 painless episodes can also be documented</td>
</tr>
</tbody>
</table>

(Reproduced from Cohn 1985 with permission.)
2.3.2 Effort Angina
Holter ECG can be used to detect ischemic changes and to examine the frequency of transient ST-segment changes in daily life, as well as the timing of onset, severity of ST depression, relationship with the heart rate, and circumstances in which ischemic changes occur. It is also useful for identifying arrhythmias associated with episodes of myocardial ischemia. In patients with stable angina, Holter ECG has a 20–45% probability of detecting myocardial ischemia, and the presence of myocardial ischemia is reported to be associated with future coronary events. However, the limitations of Holter ECG make it difficult to assess the site or severity of ischemia. In addition, recording for 48 hours rather than 24 hours is more likely to identify an attack.

2.3.3 Vasospastic Angina
This disease is essentially unstable angina, corresponding to Class II (subacute rest angina) or Class III (acute rest angina) in the classification, and must therefore be evaluated promptly. In many cases, the diagnosis can be made by taking a detailed history of the event, and Holter ECG is useful for confirming the diagnosis based on the electrocardiographic findings at the time of symptoms. Among patients with vasospastic angina, only about 20–30% exhibit ST changes associated with chest pain, and asymptomatic coronary artery spasm is common. During an attack, electrical alternans or lethal arrhythmias such as ventricular tachycardia and ventricular fibrillation may occur. When this disease is suspected based on symptoms or the history, it is desirable to record a V5-like lead in combination with any of the II, III, or aVF-like leads representing the electrical activity of the lower axis of the heart, which tends to reflect electrocardiographic changes caused by spasm of the right coronary artery. If possible, multichannel or 12-lead Holter ECG should be recorded rather than a 2-channel electrocardiogram. In addition, recording for 48 hours rather than 24 hours is more likely to identify an attack.

Holter ECG is also used to evaluate the response to treatment after diagnosis. In patients with this vasospastic angina, transient myocardial ischemia usually occurs from around midnight to the early morning. Hence, Holter ECG is the best option for detecting these electrocardiographic changes, and vasospastic angina seems to be the most suitable indication for use of Holter ECG. In the active phase, it is often necessary to record Holter ECG twice or more per month after hospitalization in order to evaluate the effect of antianginal drugs. However, it should be noted that Holter ECG is currently permitted only once a month in Japan as a healthcare service covered by health insurance.

2.4 Future Challenges
Currently, continuous recording of Holter ECG for an extended period is the most widely used method of ambulatory ECG, and a digital card or built-in memory is used for recording data. These devices allow automatic and continuous recording for a long time. In addition to the role of Holter ECG in evaluation of transient ST changes associated with coronary heart disease, it is useful for determining the time period during which acute myocardial infarction, angina pectoris, and cardiac death occur from the perspective of chronobiology, and in assessment of autonomic nervous system activity and for estimation of the prognosis by analysis of heart rate variability. It is expected that the accuracy of diagnosing coronary heart disease can be improved by use of 12-lead Holter ECG recording systems.

An event-triggered device, which is designed to be carried for several days to detect infrequent events, has also been developed, as well as a transmitting device capable of transmitting the electrocardiogram in case of emergencies. In the future, it will be important to use the most appropriate portable electrocardiographic device according to the type of cardiac events and the objectives. It is also important to consider the aspect of medical cost efficiency.


SAE is a method of detecting the ventricular late potentials (LPs), which are the delayed potentials at the end of the QRS complex, by summing and averaging tiny electrocardiographic signals that cannot be recorded with conventional surface ECG. The ventricular LPs reflect depolarization (conduction) abnormality because they are part of the QRS complex, and the LPs are therefore used as a predictor of lethal arrhythmias or sudden cardiac death. It is a simple test and widely used in Japanese hospitals specializing in cardiology.

3.1 Signal-Averaged Electrocardiography

3.1.1 Characteristics and Technical Aspects
SAE involves recording tiny potentials from the body surface that can otherwise only be recorded from the cardiac chambers. This is made possible by averaging multiple electrocardiographic waveforms together with processing to reduce noise. When ventricular LPs are recorded (Table 12), it is judged that a sustained ventricular arrhythmia is likely to occur. SAE was approved as a method for predicting lethal arrhythmia that is covered by insurance in the 2012 revision of remuneration for medical services.

To detect ventricular LPs by SAE, the X, Y, and Z leads are first recorded for at least 90–150 beats and then are summed and averaged. Next, the summed and averaged electrocardiogram is filtered and 3-lead electrocardiograms are synthesized to produce a spatial (vector) magnitude electrocardiogram. Thus, it is possible to detect the small LPs at the end of the QRS complex. In recent years, it has become possible to perform SAE analysis by averaging the Holter ECG waveforms. The standard for a positive test differs among manufacturers of SAE units. It should be noted that patients with bundle branch block are excluded. The presence of right or left bundle branch block inevitably prolongs the QRS complex, often with extension of LAso, as well, and this causes a positive result.

3.1.2 Significance in the Diagnosis of Chronic Coronary Heart Disease
The mechanism underlying sustained arrhythmia is reentry. Reentrant arrhythmias (especially sustained ventricular tachycardia) sometimes occur after myocardial infarction, and can be fatal. Existence of unidirectional block and conduction delay are both required for reentry to be
established. Unidirectional block cannot be identified before the arrhythmia is established. In contrast, conduction delay can be confirmed by the presence or absence of ventricular LPs. Thus, the LPs were used to predict the risk of hazardous, sustained ventricular tachycardia and sudden cardiac death. When stratified by the underlying heart disease, the predictive value of ventricular LPs has been best established after myocardial infarction. However, clinical research has been published that did not confirm the usefulness of the LPs for predicting sudden cardiac death (mainly caused by ventricular fibrillation) in patients with CAD, so their reliability is not rated as highly as in the past.

### 3.1.3 Future Challenges
Ventricular LPs were frequently used to predict sustained ventricular tachycardia after myocardial infarction until about the year 2000. In recent years, however, it has become clear that there are more useful predictors. Hence, LPs are less commonly investigated alone, and more often combined with other noninvasive predictors.

### 3.2 T-Wave Alternans
TWA is beat-to-beat variation in the polarity or amplitude of the T-wave (ABABAB...). It can be detected noninvasively at the microvolt level. TWA reflects abnormal ventricular repolarization and is used as a predictor of lethal arrhythmias or sudden cardiac death. Albeit it is a simple test, it is mainly performed at hospitals specializing in arrhythmia because it requires exercise testing and the electrodes are relatively expensive.

#### 3.2.1 Characteristics and Technical Aspects
TWA is often observed just before the onset of ventricular fibrillation. The measurement of TWA is based on the hypothesis that patients at risk of ventricular fibrillation should have low-level TWA even in the stable phase. Much evidence has been published about microvolt TWA (M-TWA) measured by spectral analysis of electrocardiograms recorded during exercise. Measurement of M-TWA (Table 13), which requires an exercise test, was approved for prediction of lethal arrhythmia as an item covered by health insurance in the 2012 revision of remuneration for medical services. Because there is a heart rate threshold for the appearance of TWA, it is necessary to increase the heart rate to a certain level (=110–120 beats/min) by exercise with an ergometer or treadmill at the time of measurement. Pacing may be used, but this is only possible with atrial pacing. The criteria for M-TWA positivity are an alternans voltage (alternating potential: a parameter reflecting the extent of TWA) of ≥1.9, and an alternans ratio (a parameter representing the reliability of data as the ratio of the alternating potential to background noise) >3.0 in leads X, Y, Z or the adjacent chest leads that occur at a heart rate ≤110 beats/min and persist for ≥1 min. If these criteria are not satisfied, the result is negative. If a definite judgment cannot be made, the result is classified as undeterminable.

In patients with persistent atrial fibrillation or frequent extrasystoles, it is difficult to detect alternans and therefore analysis is impossible. Because there is a heart rate threshold for the appearance of TWA, the measurement needs to be performed after the heart rate has been increased by performing exercise. However, the heart rate cannot be increased to the desired level in patients who have severe bradycardia or are on β-blockers, leading to “undeterminable” results.

#### 3.2.2 Significance in the Diagnosis of Chronic Coronary Heart Disease
There is considerable evidence about the usefulness of M-TWA in patients with heart diseases such as myocardial infarction and ischemic cardiomyopathy. It has been shown to be useful for predicting sudden cardiac death in patients with myocardial infarction, regardless of their cardiac function. Large clinical trials have been performed that only enrolled patients with poor cardiac function, and these showed that M-TWA is more useful for predicting

### Table 12. Parameters for Measuring Ventricular LP and Its Determination for Positivity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Meaning</th>
<th>Determination</th>
</tr>
</thead>
<tbody>
<tr>
<td>fQRS (ms)</td>
<td>Filtered QRS duration</td>
<td>Total time for ventricular depolarization</td>
<td>&gt;135ms</td>
</tr>
<tr>
<td>RMS40 (μV)</td>
<td>Root mean square voltage of the potential at the terminal 40 ms of the QRS complex</td>
<td>Level of low potential at the end of ventricular depolarization</td>
<td>&lt;15μV</td>
</tr>
<tr>
<td>LAS40 (ms)</td>
<td>Duration of a low amplitude potential &lt;40μV at the end of the QRS complex</td>
<td>Duration of low potential at the end of ventricular depolarization</td>
<td>&gt;39ms</td>
</tr>
</tbody>
</table>

When ≥2 of the 3 criteria (fQRS >135 ms, RMS40 <15 μV, and LAS40 >39 ms) are met, ventricular LP is determined as positive.

### Table 13. Parameters for Measuring M-TWA With Exercise Loading and Its Determination for Positivity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Meaning</th>
<th>Determination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternans voltage (μV)</td>
<td>Parameter potential: a parameter reflecting the extent of TWA</td>
<td>Degree of alternating potential in ventricular repolarization</td>
<td>&gt;1.9 μV</td>
</tr>
<tr>
<td>Alternans ratio</td>
<td>Parameter representing the reliability of data as the ratio of the alternating potential to background noise</td>
<td>Reliability of alternating potential in ventricular repolarization</td>
<td>&gt;3.0</td>
</tr>
</tbody>
</table>

When both criteria (alternans voltage >1.9 μV and alternans ratio >3.0) are met, M-TWA is determined as positive.
all-cause death or cardiac death than for predicting lethal ventricular arrhythmias. There have been recent reports about the usefulness of detecting TWA by Holter ECG in patients with myocardial infarction and ischemic cardiomyopathy.

### 3.2.3 Future Challenges

Two new methods of detecting TWA have recently become available and are already in clinical use. One is a simple method of detecting TWA continuously over 24 hours by using time-domain analysis to determine the modified moving average (MMA) of Holter ECG data (MMA-TWA). However, there is insufficient evidence about the usefulness of these methods, and this is a subject for future research.

### 3.3 Body Surface Potential Mapping

The current reference system is the 87-lead method developed by Watanabe et al. It is used to identify the site and severity of myocardial ischemia and infarction, and to evaluate the risk of ventricular arrhythmia.

#### 3.3.1 Characteristics and Technical Aspects

Body surface potential mapping involves collection of electrocardiographic information from the surface of the thorax (precordium and back), which makes it different from vectorcardiography (fixed electrical potential) or standard 12-lead ECG (fewer leads and some bipolar leads). This test is covered by health insurance.

The device manufactured by Fukuda Denshi is currently the standard system used in Japan. Its 87 leads are arranged mainly in the precordial region and a few on the patient’s back by surrounding the chest wall using sheets with 13 rows of electrodes (A–M), and potentials are recorded with Wilson’s central terminal electrode as the indifferent electrode. Columns A, E, and I are placed on the right midaxillary line, midsternal line, and left midaxillary line, respectively, while columns B, C, and D are placed so that columns A and E are equally divided into 4. Similarly, columns F, G, and H are arranged so that columns F and I are equally divided into 4. Column J is positioned so that the distance between columns I and J is equal to the distance between columns H and I.

In the same manner, column M is positioned so that the distance between columns M and A is equal to the distance between columns A and B. With regard to positioning of the rows, rows 6 and 4 are placed on the midline of the sternum at the level of the second and fifth intercostal spaces, respectively, and then row 5 is placed between rows 6 and 4. Rows 7, 3, 2, and 1 are positioned so that the space between each row is equal. Rows 6 and 7 do not exist in columns A and I located in the axillary regions. Thus, body surface potentials must be recorded using specialized sheet electrodes, the supply of which is gradually shrinking because a new product has not been developed.

#### 3.3.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

Body surface potential mapping can provide detailed information on the location and extent of myocardial infarction and myocardial ischemia. The map is the most frequently used display method, because it allows diagnosis of myocardial infarction that is impossible to diagnose with standard 12-lead ECG. Localization of ischemic regions is also improved by recording T-wave and ST-segment electrograms. The map contributes to accurate quantitation of the infarcted area. In addition, it is possible to estimate the location of regions of ischemic myocardium by creating an ST-T map, which can also be used to assess the risk of severe ventricular arrhythmia. The isochrone map can be used to evaluate ischemic regions after exercise.

### 3.3.3 Future Challenges

Although body surface potential mapping is covered by health insurance, it is currently only used at a few institutions. The reasons are that recording and analysis are troublesome, and even maintenance is not easy because new models are not being developed. Moreover, other modalities that can directly evaluate cardiac morphology and function, such as echocardiography, cardiac MRI, and radionuclide imaging, have become more important for diagnosis.

### 3.4 Magnetocardiography

#### 3.4.1 Characteristics and Technical Aspects

Because magnetocardiography directly measures the magnetic fields generated by electric currents in the heart, there is no distortion of information such as occurs with ECG (P wave, QRS complex, and ST segment), and the sensitivity is higher than that of electrocardiograms obtained by measurement of electrical potentials. The location of the current source can be easily estimated by extracting information on the myocardial current just beneath the sensor. As body surface electrodes are not required, it is unnecessary to filter the direct current component of the signal, and deviation can be evaluated as an absolute value relative to the ST segment. Magnetocardiography became covered by health insurance in 2003.

To perform magnetocardiography, a special superconducting magnetic sensor called a superconducting quantum interference device (SQUID) is used to measure tiny magnetic fields generated on the body surface as the heart beats. The information thus obtained can be used to display an image of the heart, as with echocardiography or cardiac radionuclide imaging. Thanks to technical advances, it is also possible to display 3-dimensional images using devices manufactured by Hitachi High-Technologies. Multichannel devices that can cover the entire heart simultaneously are becoming increasingly popular, solving the problems of spatial positioning accuracy and reproducibility between sensors, and noninvasive noncontact measurement can now be performed while the subject is wearing clothing.

#### 3.4.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

Magnetocardiograms can be displayed as a time waveform map, magnetic field (distribution) map, current arrow map, current integral map, current ratio map, etc. The time waveform map displays the magnetic field strength as a waveform similar to an electrocardiogram, and can be used to accurately evaluate ST-segment deviation (an ischemic change). By summing and averaging to detect very weak signals, the substrate of ventricular tachycardia can also be examined. It is also possible to evaluate the existence of regions of infarcted and ischemic myocardium that are difficult to diagnose by body surface ECG.

The current arrow map delineates the current at each
point as a vector arrow based on the magnetic field gradient (spatial difference) between 2 adjacent points, and it is useful for estimating the origin of extrasystoles. It is also useful for diagnosis of other comorbidities. The greatest advantages of echocardiography are that it is simple to perform and relatively easy to repeat. It has been reported that detection of cardiac dilatation and dysfunction by resting echocardiography has prognostic significance in patients with chronic coronary heart disease, especially those who have hypertension or valvular disease. It is also useful for diagnosis of other comorbidities. The greatest advantages of echocardiography are that it is simple to perform and relatively easy to repeat. It has been reported that detection of cardiac dilatation and dysfunction by resting echocardiography has prognostic significance in patients with chronic coronary heart disease, especially those who have hypertension or diabetes presenting abnormalities on ECG. Echocardiography is not recommended for routine assessment of cardiac function in patients with normal ECG, no history of myocardial infarction, no symptoms suggesting heart failure, no complex ventricular arrhythmia, and no symptoms suggesting cardiac diseases. Repeated evaluation of cardiac function by echocardiography is not recommended for patients without any changes in clinical status, for whom no change in therapy is planned, and with low risk for cardiovascular events.

### 3.4.3 Future Challenges

Magnetocardiography is characterized by rapid noninvasive acquisition of data while the subject remains clothed, and provides a large amount of information. However, it is not a widely used test, possibly because no consensus has been established about the methods of measurement and analysis and because the equipment is expensive. Currently, it is only used at a few centers in Japan. Recommendations and levels of evidence for SAE, TWA, body surface potential mapping and magnetocardiography are shown in Table 14.

### 4. Resting Echocardiography

#### 4.1 Significance in the Diagnosis of Chronic Coronary Heart Disease

Resting echocardiography provides information on the treatment and prognosis of patients with chronic coronary heart disease, especially those who have hypertension or valvular disease. It is also useful for diagnosis of other comorbidities. The greatest advantages of echocardiography are that it is simple to perform and relatively easy to repeat. It has been reported that detection of cardiac dilatation and dysfunction by resting echocardiography has prognostic significance in patients with chronic coronary heart disease, especially those who have hypertension or diabetes presenting abnormalities on ECG. Echocardiography is not recommended for routine assessment of cardiac function in patients with normal ECG, no history of myocardial infarction, no symptoms suggesting heart failure, no complex ventricular arrhythmia, and no symptoms suggesting cardiac diseases. Repeated evaluation of cardiac function by echocardiography is not recommended for patients without any changes in clinical status, for whom no change in therapy is planned, and with low risk for cardiovascular events.

### 4.2 Comparison With Other Tests

Although radionuclide imaging can help to measure LVEF more accurately, it does not provide information on valvular disease. Treatment strategies are determined based on the LVEF and global assessment of cardiac contractility, regional wall motion abnormalities, diastolic function, left ventricular filling, and the presence/absence of pulmonary hypertension. If echocardiography reveals regional wall motion abnormalities in the territory of multiple coronary arteries and thus suggests coronary heart disease with extensive ischemic regions, rapid performance of diagnostic angiography is warranted, such as CCTA, or coronary angiography. The left ventricle is often poorly visualized by echocardiography in obese patients or those with pulmonary disease, prior thoracic surgery, or chest deformity. Use of an ultrasound contrast agent can improve delineation of the endocardium, but this is not covered by health insurance in Japan.

### Table 14. Recommendations and Levels of Evidence for LP, TWA, Body Surface Potential Mapping, and Magnetocardiography for the Diagnosis of Chronic Coronary Heart Disease

<table>
<thead>
<tr>
<th></th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LP</td>
<td>Iib</td>
<td>C</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>TWA</td>
<td>Iib</td>
<td>C</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>Body surface potential mapping</td>
<td>Iib</td>
<td>C</td>
<td>C1</td>
<td>IVb</td>
</tr>
<tr>
<td>Magnetocardiography</td>
<td>Iib</td>
<td>C</td>
<td>C1</td>
<td>IVb</td>
</tr>
</tbody>
</table>

**COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.**
or pericardial disease. Exposure to radiation is another problem. Not all institutions can perform cardiac MRI, but it can assess cardiac function more accurately and provide information on myocardial and valvular structures. Cardiac MRI can also assess the viability of myocardium based on late gadolinium enhancement (LGE), and evaluation of cardiac function and structure is more accurate than with cardiac CT. Although radiation exposure with CT has been reduced markedly over the years, CT and radionuclide imaging are still somewhat problematic to perform in patients with a low probability of disease or younger patients.

Echocardiography also has the advantage that it can be easily performed at the bedside.

### 4.3 Indications

As described above, much information can be obtained from resting echocardiography and it should be the initial test in patients with suspected coronary heart disease. Because of its simplicity and noninvasiveness, echocardiography is often performed in patients for whom it is not necessary, which places a burden on the staff of institutions and may even lead to lost opportunities to examine other patients who may have benefitted from echocardiography. In recent years, indications for the appropriate use of echocardiography have been proposed. Guidelines for appropriate use of resting echocardiography are not only for primary care but also for specialist centers.

Resting echocardiography is considered appropriate if the patient has symptoms, such as chest pain, or dyspnea, or if the results of radiographic, electrocardiographic, or laboratory tests suggest cardiac disease during initial assessment or follow-up. On the other hand, it is considered inappropriate for routine assessment of cardiac function during follow-up of patients with known coronary heart disease and no changes in their symptoms or clinical findings. Conversely, echocardiographic evaluation is appropriate for acute chest pain or hemodynamic instability. To aid in the appropriate implementation of resting echocardiography while taking the above indications into account and avoiding overuse, specific guidelines for Japan have been proposed based on guidelines from Western countries.

### 4.4 Information Obtained

#### 4.4.1 Left Ventricular Systolic Function

The American Society of Echocardiography guidelines suggest that the left ventricle should be divided into 16–18 segments.
segments to assess regional wall motion (Figure 1).

The anterior septum, inferior septum, inferior wall, inferolateral wall, anterolateral wall, and anterior wall are located counterclockwise from the anterior insertion of the free wall of the right ventricle to the interventricular septum at the base and mid-left ventricle. The inferior septum has traditionally been called the septum, and the inferolateral wall and the anterolateral wall were termed the posterior wall and lateral wall, respectively. Because these old terms are still used in many situations in Japan, a table comparing the new and old terms has been provided (Table 16). If the cardiac apex is divided into 6 segments in the same way as the basal region and the mid-left ventricle, this results in a total of 18 segments. If the apex is only divided into 4 segments, it is divided into 4 segments counterclockwise from the posterior insertion of the free wall of the right ventricle to the interventricular septum at the base and mid-left ventricle.
segments (septum, inferior wall, lateral wall, and anterior wall), there are 16 segments in total, while adding an apical cap segment results in 17 segments.

Wall motion is generally assessed on a 4-point scale: (1) normokinesis or hyperkinesis; (2) hypokinesis (reduced wall thickening); (3) akinesis (no/negligible increase in wall thickness, e.g., myocardial scarring); and (4) dyskinesis (reduced systolic wall thickening and distension). When wall motion is evaluated, each segment should be assessed in multiple sections. In general, 2-dimensional echocardiography is recommended for measurement of left ventricular volume and LVEF by the modified Simpson’s method in the 4- and 2-chamber views.

4.4.2 Left Ventricular Diastolic Function
It is known that cardiac diastolic function is a prognostic indicator that is independent of left ventricular systolic function. For evaluation of diastolic function, it is recommended to measure mitral flow parameters, such as the E wave, E wave deceleration time (E-Dct), A wave, and e’ wave (by tissue Doppler imaging; mean of the septal and lateral wall values), as well as determining the E/e’ ratio, the left atrial volume corrected by body surface area, and tricuspid regurgitation (Figure 2).133

4.4.3 Direct Visualization of Coronary Flow (Doppler Echocardiography)
Coronary blood flow can be recorded by transthoracic Doppler, especially the blood flow velocity waveform in the distal left anterior descending artery.134 It is a minimally invasive and useful test, but this technique is not necessarily available at all centers.

4.4.4 Myocardial Viability
Tests that are useful for diagnosing myocardial viability include stress echocardiography, cardiac MRI, SPECT, and FDG-PET. In addition, myocardial thinning and increased brightness on resting echocardiography also suggest poor viability.

4.4.5 Mitral Regurgitation
When cardiac dysfunction occurs and results in left ventricular dilation, it causes mitral tethering that leads to functional and ischemic mitral regurgitation. Regurgitation is judged to be functional/ischemic if the systolic closing position of the leaflet is displaced towards the apex (so-called tenting). Even mild functional and ischemic mitral regurgitation may worsen the prognosis.135 Mitral regurgitation associated with exacerbation of heart failure is known to be improved by treatment, and it should be re-evaluated after the patient has been stabilized.136

4.4.6 Left Ventricular Mural Thrombus
Left ventricular mural thrombus is also detected by echocardiography. It commonly occurs in regions with decreased wall motion. If mural thrombus is suspected, it is also necessary to obtain images that differ from typical cross-sections.

4.5 Future Challenges
It has been reported that evaluation of myocardial perfusion by echocardiography using contrast medium provides equivalent results to those obtained with radionuclide imaging. However, this method is not widely used in Japan because of current restrictions on its use.137

5. Stress Echocardiography
The increase in function that occurs in response to a load is the functional reserve, and tests that involve applying a load to examine this reserve are known as stress tests. In patients with coronary heart disease, the peripheral CFR is reduced beyond the site of stenosis, and wall motion abnormalities are induced by ischemia when stress is imposed. In the context of diagnosis and treatment of chronic coronary heart disease, stress tests are often carried out to detect coronary artery stenosis and evaluate the cardiac reserve. When echocardiography is used for such evaluation, it is called stress echocardiography, and this method is characterized by the ability to not only evaluate regional wall motion abnormalities but also changes in overall cardiac function.

5.1 Characteristics and Technical Aspects
Stress echocardiography allows repeated noninvasive evaluation of changes in cardiac hemodynamics, mainly by using tomographic and Doppler methods. The heart rate and respiratory rate increase during exercise, and images are unstable, making evaluation of wall motion more difficult than at rest. In order to overcome these limitations, a quantitative assessment of wall motion is performed using automatic tracing of the endocardial surface, and a method that involves comparison of wall motion in each loading phase by viewing multiple digital images on a screen has also been introduced. Because the reliability of quantitative assessment remains problematic, visual evaluation of wall motion by an examiner viewing multiple digital images is often adopted for evaluation. Visualization of the endocardial surface has been greatly improved in recent years with advances in ultrasonic diagnostic equipment.

Tissue Doppler imaging is also used for evaluation of wall motion abnormalities during stress echocardiography.138 However, tissue Doppler imaging cannot exclude potential effects caused by movement of the entire heart or traction by adjacent healthy myocardium, and has limitations, such as the velocity recorded being dependent on the angle between the ultrasound beam and the moving direction of the region of interest. To overcome such disadvantages of the tissue Doppler method, strain imaging by 2- and 3-dimensional speckle-tracking echocardiography have been introduced for detection of ischemic regions and evaluation of myocardial viability.139,140 The loading methods for stress echocardiography in patients with chronic coronary heart disease are shown in Table 17.141–144 Dynamic

| Table 17. Methods of Stress Echocardiography (Including Unlisted for Insurance) |
|---------------------------------|-----------------------------|
| 1. Exercise stress              | 1) Dynamic stress (ergometer, treadmill, etc.) |
| 2. Pacing stress                | 2) Isotonic stress (handgrip, etc.) |
| 3. Pharmacological stress       | 1) Sympathetic agonist (dobutamine, isoproterenol, etc.) |
|                                 | 2) Coronary vasodilator (dipyridamole, ATP, etc.) |
methods are more physiological, but recording during exercise is difficult if a treadmill is used. Therefore, it is necessary to obtain images in a relatively short time immediately after the completion of exercise, but it is often difficult to get good images due to the increased respiratory rate. On the other hand, image acquisition is possible during exercise if the patient uses a bicycle ergometer in the supine or semi-sitting position, and it is also possible to assess the level of loading at which wall motion abnormalities appear. Pharmacological stress loading has the advantage that recording images at each stage is relatively easy because the position of the subject is constant. Dobutamine is the preferred stress agent because it is useful for both detection of ischemia and assessment of myocardial viability.

5.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

5.2.1 Purpose
In patients with chronic coronary heart disease, the primary purpose of stress echocardiography is to detect and assess the severity of significant coronary artery stenosis inducing ischemia. It is also used to predict the prognosis and to assess myocardial viability after recanalization (reperfusion) therapy. That is, stress echocardiography is also used to determine whether resting cardiac dysfunction can be improved by PCI.

5.2.2 Advantages and Disadvantages
In patients with chronic coronary heart disease, stress testing is used to induce myocardial ischemia and investigate its severity and extent. Exercise ECG is often used for such assessment. However, in patients with ST-T wave abnormalities, bundle branch block, or left ventricular hypertrophy at rest, the adequacy of ECG for assessment of ischemia is doubtful. Stress echocardiography is more sensitive and specific for diagnosing myocardial ischemia than stress ECG because echocardiography allows direct visualization of the presence, severity, and distribution of ischemic wall motion abnormalities.

Compared with stress radionuclide imaging, stress echocardiography is simpler and cheaper to perform because it does not require expensive equipment or difficult-to-handle radiopharmaceuticals. The disadvantages of stress echocardiography are that recording good images is difficult in a certain percentage of patients, and that results are highly dependent on the echocardiographer’s skill. These factors are probably the main reasons for the large variation in the sensitivity and specificity of this method among different centers.

5.2.3 Results and Their Significance
a. Diagnosis of Coronary Artery Stenosis
The site of myocardial ischemia can be evaluated by assessing wall motion abnormalities (and their distribution) that are triggered by loading. Detection sensitivity is higher in patients with multivessel disease than in those with single-vessel disease, and it is also higher in patients with ≥70% stenosis than in those with <70% stenosis. Moreover, detection sensitivity is higher in patients with resting regional wall motion abnormalities. The presence, distribution, and extent of myocardial ischemia revealed by stress echocardiography provide useful information for determining the indications for cardiac catheterization. A negative test is associated with a low risk of future cardiac events. Assessment of microvascular function by measuring the CFVR using transthoracic Doppler echocardiography has been introduced. The problems with this method are that measurement of CFVR for the 3 major coronary arteries is impossible in some patients, and that it is not possible to evaluate lesions distal to the site of imaging.

b. Evaluation of Myocardial Stunning
If myocardium in the ischemic region is viable, revascularization can improve left ventricular wall motion, and this includes both stunned and hibernating myocardium. Stunned myocardium is viable, but shows long-term functional abnormalities after alleviation of acute ischemia, whereas hibernating myocardium displays chronic depression of contraction due to reduced coronary blood flow. The function of hibernating myocardium can be improved by increasing the myocardial oxygen supply relative to demand, but the clinical problem associated with myocardial stunning is persistent cardiac dysfunction after early reperfusion therapy for acute myocardial infarction. Accordingly, assessment of myocardial viability is critical for predicting the prognosis and selecting treatment modalities.

Against this background, clinical evaluation of stunned myocardium by low-dose dobutamine stress echocardiography has been reported. It is also possible to detect residual myocardial ischemia by simultaneous high-dose dobutamine challenge. Dobutamine stress echocardiography can evaluate both myocardial viability and myocardial ischemia in a single examination, and it is useful for selecting patients with viable myocardium and potential myocardial ischemia and in determining the indications for revascularization. It has been reported that strain imaging is superior for assessing regional wall motion in comparison with visual evaluation of wall motion and tissue Doppler imaging, and thus can more sensitively evaluate myocardial viability.

c. Evaluation of Hibernating Myocardium
Clinically, hibernating myocardium can make it difficult to determine the indications for coronary revascularization when left ventricular dysfunction is associated with severe coronary artery stenosis. PET and thallium (Tl)-201 myocardial perfusion imaging have been used for the diagnosis of hibernating myocardium. These methods determine myocardial viability based on myocardial perfusion and metabolic activity. Animal studies have shown that dobutamine challenge can identify the contractility of hibernating myocardium, as in the case of stunned myocardium, and low-dose dobutamine stress echocardiography is used clinically to detect hibernating myocardium. However, it should be noted that there is a theoretical inconsistency in attempting to assess the contractility of failing myocardium with chronic hypoperfusion by administration of a positive inotropic agent that can aggravate myocardial ischemia during prolonged hypoperfusion. In other words, dobutamine challenge may exacerbate myocardial ischemia and thus reduce wall motion (with the contractile response being hidden) despite the presence of viable myocardium.

d. Prediction of the Prognosis
Determining the presence/absence of myocardial ischemia during exercise or pharmacological stress echocardiography
is useful for prediction of the prognosis. A negative result of stress echocardiography is associated with a low incidence of future cardiac events. Stress echocardiography is more specific for detecting myocardial ischemia than typical treadmill ECG. Even when exercise ECG is positive, it has been reported that the incidence of cardiac events is low if there is no abnormal wall motion on stress echocardiography. In contrast, patients with a positive result for stress echocardiography are more likely to develop fatal or nonfatal cardiac events.

### 5.2.4 Diagnostic Value of Various Stress Loading Methods

Currently, digitized imaging information obtained during stress echocardiography can be stored, allowing comparative evaluation of wall motion before and after loading, using images displayed in multiple windows on the same screen. The reliability of visual evaluation of wall motion was dramatically improved after this technique was introduced. The loading methods generally consist of exercise or pharmacological stress, with dobutamine or vasodilators being used as the pharmacological agents. Vasodilators include dipyridamole and adenosine, and these agents induce myocardial ischemia via the steal phenomenon. Thus, vasodilators are suitable for radionuclide myocardial perfusion imaging, which is excellent for detecting imbalances in blood flow distribution. However, induction of wall motion abnormalities by vasodilators is less frequent than with dobutamine, so dobutamine is generally used for detection of coronary artery stenosis based on wall motion abnormalities. The accuracy of the various loading methods for detecting coronary heart disease is shown in Table 18.

### 5.3 Future Challenges

A problem with using stress echocardiography to diagnose coronary heart disease is that it is not possible to sufficiently obtain good images in all patients. Moreover, evaluation of wall motion is performed by visual analysis, resulting in

### Table 18. Diagnostic Accuracy of Various Stress Tests

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise stress ECG</td>
<td>55–80</td>
<td>70–90</td>
</tr>
<tr>
<td>Stress cardiac scintigraphy</td>
<td>80–95</td>
<td>70–95</td>
</tr>
<tr>
<td>Exercise stress echocardiography</td>
<td>70–95</td>
<td>75–95</td>
</tr>
<tr>
<td>Dobutamine stress echocardiography</td>
<td>75–90</td>
<td>75–95</td>
</tr>
<tr>
<td>Dipyridamole stress echocardiography</td>
<td>45–80</td>
<td>80–95</td>
</tr>
</tbody>
</table>

(Reproduced from Koyanagi et al 1997, with permission.)

### Table 19. Recommendations and Levels of Evidence for Stress Echocardiography

<table>
<thead>
<tr>
<th>1. Diagnosis of coronary artery disease (CAD)</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Evaluation of stable chest pain</td>
<td>III</td>
<td>C</td>
<td>D</td>
<td>IVa</td>
</tr>
<tr>
<td>Possibility of CAD is moderate or more</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>b) Evaluation of acute chest pain*</td>
<td>I</td>
<td>A</td>
<td>B</td>
<td>II</td>
</tr>
<tr>
<td>Possibility of CAD is moderate, no temporal ECG ST-T changes in the absence of myocardial necrosis</td>
<td>III</td>
<td>C</td>
<td>D</td>
<td>IVb</td>
</tr>
<tr>
<td>High possibility of CAD, ECG ST-elevation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Prediction of prognosis (risk evaluation)</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post unstable AP/non-STEMI without any ischemic symptoms, heart failure symptoms, or early schedule for cardiac catheterization*</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>III</td>
</tr>
<tr>
<td>ACS, post-PCI, no symptoms, predischARGE evaluation</td>
<td>III</td>
<td>C</td>
<td>D</td>
<td>IVb</td>
</tr>
<tr>
<td>Post-PCI, ischemic symptoms (+)</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>III</td>
</tr>
<tr>
<td>Post-PCI, no symptoms, &lt;2 years since intervention</td>
<td>III</td>
<td>C</td>
<td>C2</td>
<td>IVb</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Evaluation of myocardial viability</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis confirmed by CAG, suitable for revascularization</td>
<td>I</td>
<td>A</td>
<td>A</td>
<td>III</td>
</tr>
</tbody>
</table>

*Not chronic CAD. AP, angina pectoris; CAG, coronary angiography; COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence; STEMI, ST-elevation myocardial infarction.
a marked influence of the skill and subjectivity of the analysts. To overcome this problem, more objective methods have been developed for evaluation of wall motion abnormalities, such as real-time 3-dimensional echocardiography and new technologies such as 2- or 3-dimensional strain imaging.\(^{172-175}\) and clinical application of these newer methods is increasing. Exercise echocardiography was added to the list of tests covered by health insurance in April 2012, and dobutamine stress echocardiography was included more recently in April 2018. In the future, it will be crucial to provide training so that doctors and medical sonographers become more familiar with this method in order to establish stress echocardiography as a routine examination. Recommendations and levels of evidence for stress echocardiography are shown in Table 19.

6. Myocardial Strain Echocardiography and Myocardial Contrast Echocardiography

6.1 Myocardial Strain Echocardiography

Myocardial strain echocardiography was developed for objective quantitative evaluation of regional myocardial motion by echocardiography, and analysis is performed by the tissue Doppler or speckle-tracking method. The tissue Doppler method has the problem of angle dependency (i.e., strain can only be evaluated in the direction of the ultrasound beam). In contrast, the speckle-tracking method allows analysis of strain in all regions of the left ventricle and can be applied for evaluation of the entire ventricle. It has been suggested that measurement of GLS can detect abnormalities of contractility that are not revealed by assessing LVEF, and it was recently reported that determination of GLS is useful for predicting the prognosis of various other diseases in addition to chronic coronary heart disease.

6.1.1 Characteristics and Technical Aspects

With the speckle-tracking method, the unique echocardiographic speckle pattern of a myocardial region is automatically followed on successive images by pattern matching. This method allows evaluation of myocardial strain in all regions of the left ventricle.\(^{176}\) In addition to the 2-dimensional method, a 3-dimensional speckle-tracking method that generates 3D images has become available in recent years.\(^{177}\) Because the accuracy of the speckle-tracking method is highly dependent on image quality, it is important to obtain good images for accurate measurement of myocardial strain.

Strain is an indicator of the deformation of an object and is calculated as follows: (final length–initial length)/initial length. Myocardial strain is an index that was developed to apply this concept to deformation of the myocardium, and it is a measure of how far the regional myocardium stretches or shortens in a given direction. When the left ventricular myocardium is analyzed, the end-diastolic myocardial length is used as the “initial length”. Peak systolic strain is used as an index of contractile function. A positive strain value indicates that the myocardium has stretched compared with its length at the end of diastole, and a negative strain value indicates that the myocardium has shortened.

When evaluation of regional wall motion is performed by conventional echocardiography, the change in wall thickness (i.e., movement of the myocardium in the radial direction on the short-axis image or in the transverse direction on the long-axis image) is evaluated by visual analysis. However, myocardial strain analysis also allows assessment of movement in the circumferential and longitudinal directions (Figure 3).

GLS represents the average longitudinal strain in all left ventricular segments, and was mentioned in the 2015 ASE/EACVI guidelines as a new index of global left ventricular systolic function.\(^{131}\) This index is calculated as the average of the peak systolic strains derived from 3 apical views. The normal value is reported to be approximately −20%.\(^{178}\) Because GLS has a negative value, confusion often occurs if attempts are made to express an increase or decrease in its value. Accordingly, reporting of absolute values is recommended.\(^{131}\)

6.1.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

Assessment of infarct size is important for predicting the prognosis as well as for diagnosis, and LVEF and the wall motion score index have traditionally been used for this...
purpose. In patients with acute myocardial infarction, GLS provides a more accurate estimate of infarct size than these indices. It is also useful for assessing the improvement of cardiac function and estimating the prognosis after acute myocardial infarction. A study performed in patients with chronic ischemic cardiomyopathy showed that those with an absolute GLS <11.5% had a worse prognosis than the other patients.

Recent reports have suggested that GLS is superior to LVEF for predicting the prognosis of patients with heart failure. In a prospective study of patients with chronic heart failure (including those with coronary heart disease), only GLS was a predictor of events according to multivariate analysis; LVEF and the E/e’ ratio (an index of left ventricular filling pressure) were not predictors. In addition, GLS was reported to be the best predictor of prognosis among all echocardiographic indices, even in patients who had heart failure with reduced LVEF, and was useful for risk stratification of patients with a reduced LVEF. Therefore, the measurement of GLS is recommended in patients with chronic coronary heart disease, particularly those with heart failure.

Myocardial strain analysis is also useful for evaluating left ventricular dyssynchrony. Although it is difficult to predict the occurrence of high-risk ventricular arrhythmias in patients after myocardial infarction, a dyssynchrony index derived from strain analysis can predict the occurrence of such arrhythmias independently of LVEF. In both experimental and clinical settings, it was found that myocardial layer-specific strain analysis could distinguish between no infarction, subendocardial infarction, and transmural infarction.

6.1.3 Future Challenges
Standardization of GLS among vendors has been attempted, and has reached the point where such differences are less problematic. On the other hand, differences in the determination of regional strain cannot be ignored, and it is therefore recommended that comparison should be performed with the software of a single vendor for assessment of regional strain. Because the myocardium moves three-dimensionally, there are limitations to evaluation of myocardial strain based on 2D images, and 3D speckle-tracking analysis is desirable for more accurate evaluation. However, 3D imaging currently achieves lower spatial and temporal resolution than the 2D method, suggesting the need for improvement in the future.

6.2 Myocardial Contrast Echocardiography
Myocardial contrast echocardiography is a method of evaluating myocardial perfusion on echocardiograms by using the ultrasound enhancing agent. The ultrasound enhancing agent is a solution containing microbubbles, and the myocardial signal intensity is enhanced by these microbubbles flowing through the microcirculation. Although myocardial contrast echocardiography is not widely used, because no contrast media are covered by health insurance for evaluation of myocardial perfusion, it is not only possible to directly visualize the coronary microcirculation, but also to quantitatively evaluate myocardial blood volume, flow rate, and myocardial blood flow.

6.2.1 Characteristics and Technical Aspects
Microbubbles in the ultrasound enhancing agent (air or fluorocarbon gas) pass through the capillaries in the same way as red blood cells, so the myocardial contrast enhancement obtained by this method is an indicator of the myocardial microcirculation (mainly the capillary bed). When intracoronary injection is performed, myocardial contrast enhancement can easily be obtained. However, myocardial contrast enhancement cannot be obtained in the standard echocardiographic setting when peripheral intravenous injection is performed. This is because only a small number of microbubbles enter the coronary microcirculation after peripheral injection and the ultrasound beam itself destroys bubbles in the microcirculation. Accordingly, an imaging method was devised to minimize

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**Figure 4.** Myocardial contrast echocardiography in a 71-year-old female patient with acute anterior myocardial infarction. Intracoronary myocardial contrast echocardiography was performed after reperfusion of the left anterior descending artery by PCI. (Left) Before contrast injection into the left coronary artery. (Right) After contrast injection. Although coronary angiography showed TIMI 3 flow after PCI, a contrast defect due to the no-reflow phenomenon was observed in the apex (arrows).
destruction of the microbubbles by intermittent transmission of an ultrasound pulse. In a clinical study, evaluation of perfusion by the intermittent mode yielded similar results to those of myocardial scintigraphy. A multicenter study also showed that the results of myocardial contrast echocardiography and myocardial scintigraphy were consistent.

Subsequently, high-sensitivity imaging methods were developed using multiple ultrasound pulses, such as the pulse inversion method, allowing visualization of myocardial perfusion with low acoustic pressure ultrasound that did not destroy microbubbles. When using this mode, there is no need for intermittent imaging and real-time evaluation of myocardial perfusion is possible. Real-time myocardial contrast echocardiography also allows simultaneous observation of left ventricular wall motion, which is advantageous for making a diagnosis of ischemia. However, use of a fluorocarbon gas contrast agent is essential to obtain adequate signals at a low acoustic pressure.

### 6.2.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

Myocardial contrast echocardiography is useful for quantitative assessment of the coronary microcirculation by the method of Wei et al. If the transmitted ultrasound pulse has a sufficiently strong acoustic pressure to completely destroy the microbubbles at the time of stable blood concentration, gradual extension of the interval for intermittent transmission allows more bubbles to flow into the ultrasound beam width until a plateau is reached. The relationship between the intensity of myocardial contrast enhancement and the ultrasound pulsing interval is approximated by the function \( y = A(1 - e^{-\beta t}) \), where \( y \) is the contrast signal intensity, \( t \) is the pulsing interval, \( A \) is the plateau level of contrast signal intensity, and \( \beta \) is the reciprocal of the pulsing interval \( T \) that reaches the plateau value \( A \). The curve that can be drawn from this relation is called a replenishment curve.

Because “\( A \)” derived from this function reflects the myocardial blood volume and “\( \beta \)” reflects the flow rate, the product of these values \( (A \times \beta) \) closely correlates with myocardial blood flow. Myocardial contrast echocardiography is possible with the real-time method as well as the intermittent method. In particular, noninvasive assessment of flow rate \( \beta \) is difficult using any method apart from myocardial contrast echocardiography, and it has been reported that the \( \beta \) reserve correlates well with CFR obtained by the Doppler guidewire method.

Myocardial contrast echocardiography visualizes the microcirculation, and can also estimate myocardial viability. In some patients with acute myocardial infarction, a contrast defect (the “no-reflow” phenomenon) is observed after reperfusion (Figure 4). In such cases, improvement of cardiac function in the chronic phase cannot be expected. Moreover, hemorrhagic infarction occurs at a high frequency, and the long-term prognosis is poor. It has been reported that the \( A \times \beta \) value derived from the replenishment curve can be used to estimate myocardial viability with greater accuracy than dobutamine stress echocardiography or myocardial scintigraphy in patients with chronic coronary heart disease. Recommendations and levels of evidence for strain and contrast echocardiography are shown in Table 20.

### 6.2.3 Future Challenges

Currently, the lack of ultrasound enhancing agents that can be used to assess myocardial perfusion is an obstacle to widespread adoption of myocardial contrast echocardiography. However, given that this method can not only directly visualize the myocardial microcirculation, but also makes it possible to evaluate previously unmeasurable indicators such as \( \beta \), it is expected to be used clinically when a ultrasound enhancing agent for myocardial perfusion is approved in the future.

### 7. Cardiac Radionuclide Imaging

#### 7.1 Myocardial Perfusion Imaging

##### 7.1.1 Features and Evidence

Cardiac radionuclide imaging is a noninvasive functional imaging method for patients with coronary heart disease and is widely used for diagnosis, evaluation of severity, determination of treatment strategies, and assessment of the prognosis. With cardiac radionuclide imaging, myocardial blood flow can be readily evaluated during exercise or pharmacological stress. Particularly, a major feature is that diagnosis of myocardial ischemia is possible by combining radionuclide imaging with an exercise test. Even if exercise testing is impossible or contraindicated, stress testing with a vasodilator allows safe diagnosis of coronary heart disease and risk assessment. In patients with coronary heart disease, the pretest probability based on the Bayes theorem should be considered when selecting the basic diagnostic procedures.

Both stress and resting myocardial perfusion SPECT have been widely used for diagnosis of coronary heart disease in routine clinical practice since the 1970s. Myocardial perfusion SPECT has been shown to be particularly useful in patients with a moderate pretest probability. Prognostic studies involving thousands of patients have been performed in Western countries and Japan, resulting in accumulation of extensive evidence on the usefulness of

| Table 20. Recommendations and Levels of Evidence for Strain- and Contrast Echocardiography for the Diagnosis of Chronic Coronary Heart Disease |
|-------------------------|---------|----------------|---------|----------------|
| Prediction of the prognosis using GLS | I B | B (MINDS) | I Va |
| Assessment of myocardial viability | Ilia C | B | IVb |
| Evaluation of myocardial microvascular damage | Ilia C | B | IVb |

COR, class of recommendation; GLS, global longitudinal strain; GOR, grade of recommendation; LOE, level of evidence.
myocardial perfusion SPECT for diagnosis and prognosis.

Radionuclide imaging makes it possible to noninvasively obtain information on physiological function with a trace dose of a radiopharmaceutical while not using contrast medium. Hence, this noninvasive modality can be the first choice for patients with CKD. Exposure to radiation during myocardial perfusion SPECT has been significantly reduced by the introduction of technetium (Tc)-99 m-labeled preparations with a short half-life. On the other hand, cardiac radionuclide imaging is less effective for obtaining morphological information in comparison with other imaging modalities. Accordingly, fusion imaging is performed for logical information in comparison with other imaging modalities. ECG-gated acquisition has recently become popular as a standard imaging procedure, allowing concurrent analysis of both myocardial blood flow and myocardial function. ECG-gated acquisition can be used to assess left ventricular wall motion, systolic wall thickening, left ventricular volume, LVEF, left ventricular diastolic function, and left ventricular synchrony. The following are indicators of high-risk patients, such as those with multivessel disease or left main trunk lesions: decreased wall motion with stress that reflects stunned myocardium; LVEF <45% at rest or after stress; reduction of LVEF by >5% after stress; transient left ventricular dilation (dilation by ≥10% vs. rest); increased pulmonary accumulation of the radionuclide; and visualization of the right ventricle.

7.1.2 Rest and Stress Myocardial Perfusion Imaging

The most widely used cardiac radionuclide imaging modality for diagnosis and selection of treatment strategies for coronary heart disease is stress and rest myocardial perfusion SPECT (Figure 5). Among the various radiopharmaceuticals, Ti-201 is widely used in Japan, as well as Tc-99 m MIBI and Tc-99 m Tetrofosmin, which have shorter half-lives and achieve good image quality. For stress loading, exercise (treadmill or bicycle ergometer) is used whenever possible, whereas vasodilators (adenosine, adenosine triphosphate [ATP], or dipyridamole) are used only if exercise cannot be performed or is contraindicated. In Japan, use of adenosine for stress testing is covered by health insurance. (Note: ATP and dipyridamole are not covered for use in stress myocardial perfusion SPECT by Japanese health insurance.) When stratified by the type of loading, the sensitivity and specificity of exercise myocardial perfusion SPECT for detection of significant coronary stenosis was reported to be 82–88% and 70–88%, respectively, whereas stress myocardial perfusion SPECT using vasodilators has a sensitivity of 88–91% and a specificity of 75–90%.120–223

Recently, use of a gamma camera for the heart using cadmium–zinc–telluride semiconductors as the gamma ray detector has become popular. Its sensitivity is reported to be 84–87% and its specificity is 62–86% for lesions in the left anterior descending artery, 75–84% and 84–93% for lesions in the left circumflex artery and 74–80% and 77–88% for lesions in the right coronary artery.214–216 ECG-gated acquisition has recently become popular as a standard imaging procedure, allowing concurrent analysis of both myocardial blood flow and cardiac function. ECG-gated acquisition can be used to assess left ventricular wall motion, systolic wall thickening, left ventricular volume, LVEF, left ventricular diastolic function, and left ventricular synchrony. The following are indicators of high-risk patients, such as those with multivessel disease or left main trunk lesions: decreased wall motion with stress that reflects stunned myocardium; LVEF <45% at rest or after stress; reduction of LVEF by >5% after stress; transient left ventricular dilation (dilation by ≥10% vs. rest); increased pulmonary accumulation of the radionuclide; and visualization of the right ventricle.217–221

Myocardial perfusion SPECT has prognostic value in patients with a moderate risk of coronary heart disease. Based on this classification, large-scale registry studies, clinical studies, and meta-analyses have demonstrated an extremely low incidence of cardiovascular death and nonfatal myocardial infarction when stress myocardial perfusion SPECT findings are within the normal range.222,223 In addition, the incidence of cardiac events increases in proportion to the stress perfusion deficit score calculated from SPECT images, suggesting its usefulness for predicting the prognosis (Figure 6).224–236 The incidence of cardiac events increases with an increase in the extent of ischemic myocardium, and the prognosis improves together with a decrease in ischemic myocardium after coronary revascularization. Therefore, demonstration of myocardial ischemia affecting >10% the left ventricle on stress myocardial perfusion SPECT is recommended as the indication for revascularization.127,226,227
7.1.3 Detection of Myocardial Viability
Cardiac radionuclide imaging is useful for assessing myocardial viability in patients with coronary heart disease. The presence of ischemia and the extent of blood flow reduction are usually judged by myocardial perfusion SPECT, and a high diagnostic accuracy has been shown. TI-201 is used to assess viability based on cell membrane and Na/K pump function, whereas Tc-99m assesses mitochondrial function. It has been reported that quantitative evaluation (% uptake) improves the accuracy of evaluating myocardial viability, and the threshold value is usually set at 50–60%. There have been many reports that TI-201 myocardial perfusion SPECT is useful for predicting the improvement of wall motion after revascularization. Although there are some contradictory opinions, the diagnostic sensitivity was reported to be similar or better than that of dobutamine stress echocardiography (but specificity is inferior), with TI-201 myocardial perfusion SPECT being reported to show a sensitivity of 86% and a specificity of 59%. When stress TI-201 myocardial perfusion SPECT is performed, residual viable myocardium may be underestimated by conventional delayed imaging because of insufficient redistribution, so small additional doses of the radionuclide are given or 24-hour imaging is performed as a countermeasure. Tc-99m myocardial perfusion SPECT was reported to show a sensitivity of 81% and a specificity of 66%. To prevent underestimation, sublingual nitroglycerin is considered effective. If stress myocardial perfusion scintigraphy cannot adequately assess myocardial viability, 18F-FDG-PET is an alternative imaging method for this purpose.

7.1.4 Radiation Exposure With Cardiac Radionuclide Imaging
It is necessary to optimize test methods and protocols by considering both the usefulness for diagnosing coronary heart disease and the risk of radiation exposure with cardiac radionuclide imaging. Tc-99m-labeled myocardial perfusion radiopharmaceuticals have a short half-life of 6 hours, so it is possible to reduce radiation exposure by using these agents for scintigraphy. The stress and resting protocol generally used in Japan involves administration of doses from 740 to 1,110 mSv, the whole-body dose is 6–9 mSv. Therefore, use of Tc-99m-labeled radiopharmaceuticals is recommended from the perspective of reducing exposure to radiation. However, TI-201 is recommended if intestinal accumulation was high during previous rest or in those taking digitalis, stress myocardial perfusion imaging is indicated for detecting the presence or absence of ischemia, predicting the prognosis and risk stratification based on ischemic burden, determining the indications for revascularization, judging effects of treatment, and predicting the prognosis after initiation of treatment.

a. Detection of Ischemia
When stress myocardial perfusion imaging is performed to detect ischemia, the best indication is typical angina pectoris with an intermediate or high pretest probability. If the reversible defect identified by perfusion imaging, this means moderate or high risk (see next section 7.2.2). Because exercise ECG cannot be used for diagnosis of ischemia in patients with left ventricular hypertrophy with ST depression or in those taking digitalis, stress myocardial perfusion imaging is a suitable option in such cases. Adverse reactions to adenosine and adenosine. Adverse reactions to adenosine are minor, but the incidence is high, and extracardiac accumulation in the liver and gastrointestinal tract is greater than with exercise, so artifacts are often problematic. Therefore, concomitant low-level exercise loading is also recommended because fewer adverse reactions and improvement of image quality are expected. Adenosine receptors are competitively inhibited by xanthine derivatives such as aminophylline and caffeine, and intake of caffeine-containing products should therefore be avoided for at least 12 hours before an adenosine stress test is performed. If adenosine cannot be used (e.g., in patients with bronchial asthma), a dobutamine stress test is alternatively performed. Atropine may also be used in combination with dobutamine in patients on ß-blockers to avoid underloading; the sensitivity and specificity of this method are 85% and 72%, respectively, with a diagnostic accuracy of approximately 83%.

Identification of ischemia is also an indication when severe calcification in the coronary arteries is detected, such as on chest and CCTA. Because coronary artery calcification and ischemia are positively correlated, and a CACS ≥400 corresponds to a moderate pretest probability, stress perfusion imaging should be considered. Even if the findings of stress perfusion imaging are normal, severe calcification with a CACS ≥1,000 is associated with a moderate incidence of severe coronary artery lesions requiring revascularization. Therefore, coronary angiography is indicated in such cases if the patient has chest pain. In contrast, ischemia is rare in asymptomatic patients with a CACS ≤100, and perfusion imaging is not indicated. Recently, SPECT-CT has become popular. Because visual assessment of the severity of coronary artery calcification on low-dose CT scans obtained for attenuation correction is well correlated with the CACS, assessing coronary artery calcification is recommended when CT scans are taken for attenuation correction.

With regard to diagnosis of ischemia in asymptomatic patients, stress myocardial perfusion imaging may be considered for high-risk patients with multiple coronary risk factors, patients with decreased exercise tolerance, and patients with an elevated CACS, if they have a high pretest probability, but it is not indicated for patients with a moderate to low pretest probability. The CACS is useful for risk stratification in relation to the long-term prognosis, even in asymptomatic patients, and measurement of CACS may be considered first in some cases.
the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, adenosine stress myocardial perfusion imaging was performed in 1,123 asymptomatic patients with type 2 diabetes and abnormal findings were obtained in 22%, with the frequency of moderate or severe perfusion defects increasing 5-fold as the disease duration became longer. In a 3-year prognostic study, the extent of myocardial ischemia was significantly reduced by drug therapy, demonstrating the usefulness of severity assessment and follow-up with stress myocardial perfusion imaging. Investigation of ischemia may be indicated if there are ST-T changes on ECG or wall motion abnormalities on echocardiography. However, there is no clear evidence for this, and further studies are needed in the future.

b. Significance in the Diagnosis of Chronic Coronary Heart Disease

There have been remarkable recent improvements in the accuracy of various imaging modalities for diagnosing chronic coronary heart disease. CCTA, MRI, stress echocardiography, myocardial perfusion SPECT, and PET each have advantages and disadvantages, and many reports on their diagnostic accuracy have been published. Although there may be some variation among reports, the diagnostic accuracy of the modality in which each facility has expertise is probably close to the generally reported level of accuracy. Regarding the diagnostic accuracy of stress myocardial perfusion imaging, the sensitivity and specificity are estimated to be 73–92% and 63–87%, respectively. There is generally no difference in specificity between pharmacological and exercise stress testing. However, patients who cannot perform sufficient exercise are typically tested using vasodilators, which makes the specificity of vasodilator testing higher because patients who cannot exercise adequately are more likely to have coronary heart disease. Because adenosine was administered at a dose of 140 μg/kg/min in the studies that obtained this result, the sensitivity at 120 μg/kg/min (the dose used in Japan) is probably equivalent to that of exercise testing. It should also be noted that these studies were conducted using Ti-201, which means that the sensitivity of testing with Tc-99m agents may be lower because its myocardial extraction decreases at high rates of blood flow. No clear evidence has been obtained so far, but this is a point to consider when interpreting images. Diagnostic accuracy has conventionally been calculated by comparison with anatomical stenosis of ≥50–70% on coronary angiography as the gold standard, but anatomical stenosis is not always consistent with ischemia that reflects functional stenosis. Therefore, there have recently been an increasing number of studies in which diagnostic accuracy was examined by severe stenosis (≥70%), or using a FFR <0.8 for moderate stenosis (30–70%) as the gold standard. FFR <0.8 was used as a criterion for significant coronary lesions in the EVINCI study, which enrolled patients with a moderate pretest probability. EVINCI compared diagnostic accuracy among CCTA, PET, SPECT, MRI, and echocardiography. Overall, CCTA showed the highest diagnostic accuracy with an area under the curve (AUC) of 0.91, sensitivity of 91%, and specificity of 92%, whereas SPECT achieved an AUC of 0.74, sensitivity of 74%, and specificity of 73%. When only patients with good-quality images were assessed, these numbers improved to a sensitivity of 81%, specificity of 86%, and diagnostic accuracy of 84%, which means that the diagnostic accuracy is as good as that of PET (which has the most stable diagnostic accuracy). Given that the quality of SPECT images acquired in Japanese patients usually corresponds to “good image quality” in Western countries, except when artifacts occur, the diagnostic accuracy of SPECT may be close to that of PET in Japanese patients. When CCTA, PET, and SPECT were compared in patients with suspected coronary heart disease, using FFR <0.8 as an indicator of significant coronary lesions, SPECT showed the lowest sensitivity of 57% vs. 90% for CCTA and 87% for PET, but SPECT had the highest specificity of 94% vs. only 60% for CCTA and 84% for PET. The diagnostic accuracy of CCTA, SPECT, and PET was 74%, 77%, and 85%, respectively. When diagnosis is based on the FFR, PET has the highest diagnostic accuracy and achieves stable results, and the low sensitivity of SPECT needs to be taken into consideration. In a study using a semiconductor camera, the sensitivity, specificity, and accuracy were low (52%, 68%, and 58%, respectively) when a significant lesion was defined as corresponding to ≥75% stenosis on coronary angiography. However, when “≥90% stenosis” or “<90% and ≥50% stenosis” combined with FFR <0.8 was adopted as the definition of a significant lesion, the sensitivity, specificity, and diagnostic accuracy improved to 77%, 91%, and 84%, respectively. Thus, SPECT does not always reflect anatomical stenosis, but can detect flow-limiting functional stenosis with a high level of accuracy.

Because SPECT images display the relative blood flow distribution, a weakness of this method is low detection rates for balanced ischemia caused by multivessel disease, etc. However, quantitative evaluation of myocardial blood flow has become possible with the development of semiconductor camera, and recent studies of dynamic imaging using Ti-201, when a myocardial flow reserve (MFR) ≤1.5 was used as the cutoff value for detection of left main trunk or triple-vessel disease, favorable results were obtained with a sensitivity, specificity, and diagnostic accuracy of 86%, 78%, and 80%, respectively. Quantitative evaluation of myocardial blood flow by SPECT is not suitable for routine clinical practice because of its complexity, but it allows accurate diagnosis of even balanced ischemia (which is often underestimated by conventional SPECT) in appropriate patients. Compared with MRI, SPECT has a lower sensitivity but higher specificity. MRI is considered to show a high negative predictive value, but has a low specificity. It should also be kept in mind that studies of the diagnostic accuracy of stress myocardial perfusion imaging were conducted after withdrawal of antianginal drugs, so the diagnostic accuracy (particularly the sensitivity) of this modality could be lower if testing is performed without discontinuing these drugs.

### 7.2.2 Predicting the Prognosis and Risk Stratification

There is considerable evidence on using stress myocardial perfusion imaging for predicting the prognosis. The amount of ischemic myocardium, based on the severity and extent of ischemia, is better correlated with prognosis than the severity of coronary heart disease assessed by coronary angiography, and is also strongly correlated with “hard events” such as nonfatal myocardial infarction and cardiac death. Although the incidence of events is lower in Japanese patients than in Westerners, a similar trend was confirmed by a prospective multicenter prognosis study (J-ACCESS study) with over 4,000 subjects. When stress myocardial perfusion imaging is normal, the prognosis is
good and the annual hard event rate is only approximately 0.6%, and even lower in the Japanese population. If SPECT is normal, the annual cardiac event rate is <1%, even in patients with moderate coronary stenosis on coronary angiography. This may be a reason for deciding to defer revascularization when considering whether or not revascularization should be performed. However, the predictive value of SPECT is lower than that of CFR or FFR in patients with multivessel disease. On the other hand, the high-risk SPECT findings are associated with a poor prognosis. An observational study of 2,686 patients revealed that patients with moderate or severe ischemia (equivalent to ≥10%) and a low LVEF (LVEF <30%) had an annual mortality rate 50-fold higher than patients with normal results. In general, the high-risk findings include fixed/reversible defects in multivessel territories, transient ischemic dilatation, LVEF <45%, and high pulmonary accumulation during stress loading. These findings are useful for predicting the prognosis.

The PROMISE study was a prospective randomized trial performed at 193 centers that allocated 10,003 patients with suspected stable angina to CCTA or functional testing (exercise ECG in 10.2%, stress myocardial perfusion scintigraphy in 67.5%, and stress echocardiography in 22.4%), revealing no difference between groups with regard to the 2-year event rate for myocardial infarction, death, or unstable angina/complications requiring hospitalization. However, coronary angiography and revascularization were more frequent in the CCTA group. The population studied in this investigation had a relatively favorable 2-year event rate of 3%, with nearly half of the events being hospitalization for unstable angina and a low frequency of hard events, which means that they were generally low-risk patients.

Thus, CCTA tends to overestimate the need for further intervention in low-risk patient populations, and it is not recommended from the perspective of cost-effectiveness. A multicenter randomized controlled trial (IAEA-SPECT/CCTA study) that compared CCTA and stress myocardial perfusion SPECT in patients with a moderate pretest probability who were asymptomatic or had mild chest pain showed a 49% reduction of patients undergoing subsequent evaluation in the SPECT group, indicating that SPECT can be recommended for patients with a moderate pretest probability in view of its cost-effectiveness. The J-COMPASS study investigated the prognosis of 2,878 Japanese patients with suspected or confirmed stable angina, who underwent CCTA, stress perfusion imaging, or coronary angiography as the initial test. There was no difference in the incidence of MACE between the patients undergoing CCTA and those having stress perfusion imaging, but the frequency of undergoing coronary angiography was 2.7-fold higher in patients initially undergoing CCTA. The revascularization rate was also highest in patients undergoing coronary angiography (odds ratio: 5.36), and was still higher in those having CCTA (odds ratio: 1.62) than in those undergoing stress perfusion imaging. The results of this study do not seem to recommend initial coronary angiography for patients with stable angina, and it was also shown that morphological assessment is more likely to lead to revascularization than functional assessment.

The COURAGE study compared outcomes in 2,287 patients with significant stenosis who were randomized to 2 groups (optimal medical therapy group or PCI followed by medical therapy group), and found no differences in hard event rates. However, the nuclear COURAGE substudy involving 105 patients with moderate to severe ischemia who underwent SPECT before treatment and approximately 1 year later showed that cardiac events were halved if ischemia improved by ≥5% after starting either treatment. A similar predictive value was demonstrated in a single-center Japanese investigation, which revealed that improvement of ischemia by ≥5% was associated with subsequent prognostic improvement. Furthermore, a multicenter study (J-ACCESS4 study) of 114 patients treated with medical therapy or revascularization showed that those with ≥5% improvement in the extent of ischemic myocardium had a significantly lower rate of cardiac events than those without such improvement.

In addition to interpretation of imaging findings, the clinical information is important for predicting the prognosis with SPECT. In particular, diabetes mellitus and CKD are significant adverse prognostic factors. In a Japanese study of 485 patients with type 2 diabetes who underwent SPECT (J-ACCESS2 study), a summed stress score (SSS) >9 and a low eGFR were significant predictors of events. In another study of 529 patients with CKD who underwent SPECT (J-ACCESS3 study), SSS ≥8, eGFR <15 mL/min/1.73 m², and C-reactive protein ≥0.3 mg/dL were significant predictors of events. Cardiac function is also an important prognostic indicator. According to data from the J-ACCESS study, the incidence of cardiac events was 5.6-fold higher in patients with a LVEF <45% compared with those with LVEF ≥45%. Thus, an equation for predicting the incidence of cardiac events based on the presence/absence of diabetes mellitus, eGFR, LVEF, age and sex has been derived, based on the database for the normal Japanese population and the results of the J-ACCESS study. The equation can be used to calculate the 3-year expected incidence of the composite endpoint of myocardial infarction, cardiac death, and heart failure requiring hospitalization, and it is useful for selection of treatment strategies and for providing information to patients.

An association between the findings on stress testing and the prognosis has been noted in several studies. Ischemic ST depression is rarely seen during pharmacological stress testing using vasodilators (<1%). Although there have been reports that patients with normal perfusion images have a good prognosis, even if ST depression occurs, there is a higher likelihood of indicating severe CHD. If ST depression is induced during the test, there is a high possibility of severe coronary heart disease even when perfusion is normal, and some reports indicate that the frequency of future cardiac events is high in such cases. Careful management of the patient is recommended when ST depression is observed during pharmacological stress testing, irrespective of whether or not perfusion images are normal. With regard to ischemic electrocardiographic changes during stress tests, a subanalysis of the J-ACCESS study showed that patients with ischemic electrocardiographic changes and a reversible perfusion defect on exercise testing had a higher incidence of cardiac events, while patients without a reversible perfusion defect had fewer events. Changes in the heart rate during pharmacological loading also have prognostic significance. The heart rate usually increases by ≥30 beats/min in stress tests using vasodilators.
When the increase is smaller than about 20 beats/min, however, there is a high risk of cardiac events and death, even with normal perfusion. Hence, the change in the heart rate is considered an independent predictor and attention should be paid to it. It should also be noted that β-blockers and caffeine will blunt the increase in heart rate.

### 7.2.3 Judgment of Indications for Revascularization

The primary indications for myocardial perfusion imaging before revascularization are assessment of the severity of ischemia, risk stratification and predicting the prognosis, detection of ischemia in patients with cardiac dysfunction, and evaluation of viability (including detection of stunned and hibernating myocardium). There is no indication for revascularization in the absence of ischemia, whereas the prognosis worsens with the extent of ischemic myocardium in the presence of ischemia, making it important to quantitatively or semiquantitatively assess the amount of ischemic myocardium. Particularly, when ischemia affects >10% of the total myocardium, the prognosis is poor with medical therapy and revascularization is indicated for improvement. Conversely, if <10% of the myocardium is ischemic, performing revascularization often worsens the prognosis and medical therapy is recommended. Similar results were obtained by subanalysis of the J-ACCESS study. In patients with cardiac dysfunction, detection of ischemic cardiomyopathy as the underlying disease and evaluation of myocardial viability are of importance. Dobutamine stress echocardiography, MRI, SPECT, and PET are mainly used to evaluate myocardial viability.

Among them, 18F-FDG-PET is the most accurate modality for predicting functional improvement in patients with cardiac dysfunction, and it is currently considered the gold standard. When stress myocardial perfusion imaging is performed (with TI-201 or Tc-99m), a reversible perfusion defect or ≥50% accumulation relative to the normal region is judged to indicate the existence of viable myocardium. With TI-201 imaging, even if a fixed defect is recognized, redistribution may be noted in approximately 20% by re-infusion of the radionuclide or by imaging after 24 hours, and the sensitivity of assessing myocardial viability is improved. Revascularization does not improve the prognosis in the absence of viable myocardium, whereas prognosis is favorable after revascularization of viable myocardium, even without improvement of LVEF. The STICH study indicated that evaluation of myocardial viability could identify patients who would benefit from CABG. Patients who show remodeling without viable myocardium (left ventricular end-systolic volume index [LVESVI] ≥84 mL/m2) have the worst prognosis, and progression of remodeling should also be noted. Usefulness of evaluating myocardial viability by 18F-FDG-PET was not demonstrated in patients with poor cardiac function in the PARR-2 study. However, subanalysis of the study showed that revascularization improved the prognosis in patients with a large area of hibernating myocardium. Therefore, if more than 10% of viable myocardium remains, revascularization is expected to improve survival. It has been reported that the left ventricular end-systolic volume is the only predictor of survival in coronary heart disease patients with viable myocardium and poor cardiac function, regardless of whether revascularization is performed, and that survival is unfavorable after revascularization in patients with advanced remodeling despite the presence of viable myocardium.

Myocardial perfusion imaging plays an important role in determining the indications for revascularization when CCTA and coronary angiography show moderate stenosis (≥30–70%). As noted above, the amount of ischemic myocardium closely correlates with the incidence of cardiac events, so revascularization should be actively considered when ischemic myocardium exceeds 10%. When invasively assessment of moderate stenosis is performed, revascularization should be considered if CFR is <2.0 or FFR is <0.8, but the CFR and FFR data are often inconsistent. Since the results of the FAME study and FAME 2 study were published, FFR has been used as the gold standard for revascularization and is recommended in guidelines, but CFR <2.0 is associated with a poor prognosis even in patients whose FFR is maintained. The cutoff value of FFR for ischemia is 0.75. However, further research is necessary because it was reported that the long-term prognosis of patients in the “gray zone” (FFR: 0.75–0.80) was better with revascularization, and another study showed that deferring revascularization when FFR was >0.75 led to a comparable result to deferring revascularization when FFR was >0.8. CFR is influenced by the peripheral circulation and is better correlated with the results of myocardial perfusion imaging than FFR, which is not influenced by peripheral factors. Finally, in an observational study of 5,340 patients with multivessel disease, the prognosis was better when revascularization was guided not by coronary angiography alone but by ischemia on perfusion imaging.

### 7.2.4 Evaluation of the Response and Prognosis After Treatment

Myocardial perfusion imaging has been used to assess the efficacy of revascularization. It can determine improvement in cardiac function, as well as the ischemic burden. It is also useful for assessing ischemia in the territory of the treated vessel at 6 months after PCI, and for estimating restenosis and residual stenosis. More than half of all patients with ischemia are asymptomatic after PCI, and their prognosis is better than that of symptomatic patients. Despite this, the extent of coronary disease is closely related to the extent of ischemia. The criteria for appropriate use do not recommend the performance of stress myocardial perfusion imaging in asymptomatic patients within 2 years after PCI. However, routine myocardial perfusion imaging at 5 years after PCI revealed abnormal findings in 60% of patients and most were in remote areas, suggesting new lesions. In patients with abnormal findings, MACE and hard events are more frequent, regardless of whether the patients have symptoms. Therefore, myocardial perfusion imaging may be considered at 5 years after PCI, even if the patient has no symptoms.

In the COURAGE nuclear substudy, stress myocardial perfusion imaging was performed before treatment and 0.5–1.5 years after treatment. No residual ischemia at the second examination was associated with no events for at least the subsequent 4 years, but an increase in cardiac events correlated with the level of residual ischemia. Hence, this method is useful for assessing the efficacy of treatment (residual ischemia) and for predicting the prognosis after treatment. In that study, the cardiac event rate halved when ischemic myocardium was reduced by ≥5%, demonstrating that the extent of improvement in ischemia is closely related to the prognosis. Even with medical
treatment, the prognosis can also be improved if there is a marked reduction in the extent and severity of ischemia. However, the rate of achieving ≥5% reduction of ischemic myocardium was significantly higher in the PCI group, and it can be assumed that the prognosis is improved by prior PCI when the volume of ischemic myocardium is medium or large. Recommendations and levels of evidence for myocardial perfusion imaging are shown in Table 21.

<table>
<thead>
<tr>
<th>Table 21. Recommendations and Levels of Evidence for Myocardial Perfusion Imaging for the Diagnosis of Chronic Coronary Heart Disease</th>
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<tbody>
<tr>
<td><strong>Uninterpretable ECG (complete left bundle branch block, pacing and preexcitation syndrome are suitable for vasodilation stress)</strong></td>
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<tr>
<td><strong>Abnormal stress ECG</strong></td>
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<td><strong>More than intermediate pretest probability case with typical chest pain</strong></td>
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<td><strong>Diagnosis of presence and location of residual ischemia in known CAD</strong></td>
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<td><strong>Diagnosis of location in myocardial infarction cases</strong></td>
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<td><strong>Decision-making of coronary intervention therapy</strong></td>
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<tr>
<td><strong>Atypical chest pain cases with ≥ intermediate pretest probability or CACS ≥400</strong></td>
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<tr>
<td><strong>Functional assessment of intermediate stenotic (40–75%) lesion</strong></td>
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<tr>
<td><strong>Assessment of interventional therapy</strong></td>
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<td><strong>Pharmacological stress in case of intermediate pretest probability without appropriate exercise tolerance</strong></td>
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<tr>
<td><strong>Asymptomatic cases with DM or strong family history of CAD or CACS ≥400</strong></td>
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<td><strong>Assessment of ischemia in cases of low pretest probability with chest pain</strong></td>
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<td><strong>Assessment after 5 years in cases of revascularization</strong></td>
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<td><strong>Less than intermediate pretest probability cases without symptom</strong></td>
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<td><strong>Routine assessment within 2 years after revascularization</strong></td>
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CACS, coronary artery calcium score (Agatston score); CAD, coronary artery disease; COR, class of recommendation; DM, diabetes mellitus; GOR, grade of recommendation; LOE, level of evidence.

The cardiac function indices calculated by ECG-gated SPECT show good reproducibility and a strong correlation with values obtained from other modalities. Information on left ventricular function and regional contractility obtained by analysis using this method adds value to myocardial perfusion data obtained from myocardial SPECT imaging, and the usefulness of such information has been recognized in patients with heart disease, especially ischemic heart disease. General methods for data collection and analysis are described here, as well as reference values for ECG-gated myocardial perfusion SPECT. A method for evaluating dysynchrony of cardiac contraction is also described, which is based on the left ventricular phase analysis technique that has been introduced in recent years.

### 8. Analysis of Ventricular Function by Nuclear Cardiology

Radionuclide angiography and equilibrium ECG-gated cardiac blood-pool scanning have been used to assess left ventricular function in nuclear cardiology. ECG-gated myocardial perfusion SPECT with radiopharmaceuticals has recently become widely used for assessing myocardial perfusion, and dedicated analytical software has also become readily available.[330] [332] This section describes the evaluation of cardiac function, focusing on this method. When ECG-gated myocardial perfusion SPECT is performed, left ventricular function is determined by using specialized software to analyze ventricular volume, EF, and regional wall motion, while diastolic function is assessed by using the differential volume curve.

#### 8.1 Left Ventricular Function Analysis With ECG-Gated Myocardial Perfusion SPECT

##### 8.1.1 Left Ventricular Volume and Systolic Function

ECG-gated myocardial perfusion SPECT is performed by synchronization with the R wave of the ECG for collection of SPECT data. One cardiac cycle is divided into 8–16 frames of equal duration to provide information for calculating LVEF and volume indices and for assessing regional contractility. Although ungated images are used for evaluation of myocardial perfusion, the ECG-gated SPECT data provide images for each time phase of the cardiac cycle.
cycle to allow assessment of wall motion. Various software programs for analysis of ventricular function are used clinically to process data obtained with ECG-gated myocardial perfusion SPECT,\(^\text{335,336}\) and high reproducibility of the results has been shown. The LVEF and left ventricular volume calculated by ECG-gated SPECT closely correlate with data obtained by other modalities, such as cardiac MRI, echocardiography, and CT.\(^\text{337,344}\) In general, there is no compatibility among the various software programs with regard to the absolute values obtained, and it is therefore desirable to use the same program for deciding the treatment strategies and comparison over time.\(^\text{345,346}\) The suitable radiopharmaceuticals for performing ECG-gated SPECT are Tc-99 m-labeled tracers (i.e., Tc-99 m MIBI or tetrofosmin), which have a half-life of 6 hours and provide adequate myocardial counts at a dose of 740–1,100 MBq. When a dedicated cardiac solid-state camera with high sensitivity is used, adequate images can be obtained even with short acquisition time or reduced radiopharmaceutical dose. Many of the software programs for functional analysis were specifically developed for Tc-99 m myocardial perfusion imaging, which is commonly used in Western countries.

Reference values for Japanese patients have been determined by using data from the Working Group of the Japanese Society of Nuclear Medicine. The reference values for QGS software are shown here (Table 22), but these will not apply to other programs.\(^\text{347,348}\) Tc-99 m-labeled radiopharmaceuticals for assessment of myocardial blood flow are advantageous in terms of the radiation dose and image quality, and are often used for ECG-gated SPECT. Although ECG-gated SPECT can also be performed with TI-201- or I-123-BMIPP,\(^\text{337,349,350}\) attention should be paid to the accuracy of contour extraction when there is a large defect (especially a severe defect on I-123 BMIPP images).

### 8.1.2 Left Ventricular Diastolic Function

The indices of left ventricular diastolic function can be calculated using data acquired with ECG-gated myocardial perfusion SPECT, by dividing the RR interval into 16–32 frames (usually 16 frames).\(^\text{351,352}\) With nuclear medicine, diastolic function is calculated from the derivative (differential) of the volume curve (dV/dt), and the common indices are the PFR (/s), 1/3FR mean (/s), and TPF (/ms). Although these indices will vary depending on the heart rate and the curve fitting method, the reference values for the widely used QGS software (Cedars-Sinai Medical Center, USA) are shown here (Table 23).\(^\text{347,348}\)

### 8.1.3 Wall Motion

Analysis of wall motion is performed by visual observation of dynamic images and assessment of 3-dimensional contours on tomographic images. With ECG-gated SPECT, the wall motion is calculated as the distance (mm) of endocardial motion between end-diastole and end-systole, and percent systolic wall thickening (%) is calculated from the percent increase in the wall count. Mapping of wall motion and systolic wall thickening is also performed, and related reference values are available.\(^\text{347,356}\)

### 8.1.4 Changes in Cardiac Function Under Stress

ECG-gated synchronization SPECT shows high reproducibility. In patients with severe ischemia or multivessel disease, stress-induced left ventricular dysfunction may be persistent, and so-called post-stress stunning can be detected (i.e., a transient decrease in the EF and/or left ventricular dilation after stress loading). This has been reported to be a useful index for diagnostic and prognostic evaluation.\(^\text{357,358}\) These changes are not only observed with exercise stress, but also with myocardial perfusion SPECT using coronary vasodilators such as adenosine or dipyridamole for pharmacological stress, but the underlying mechanism is not well understood. Although it has been suggested that subendocardial ischemia is involved, it should be noted that these imaging changes may not necessarily reflect actual LVEF reduction or ventricular dilation.

### 8.1.5 Phase Analysis

In nuclear cardiology, phase analysis was initiated in the 1980s. This method involves Fourier transformation of the

| Table 22. Standard Values of Left Ventricular Volume and Ejection Fraction With ECG-Gated Myocardial Perfusion SPECT |
|---------------------------------|----------------|-------------------|
|                                | Male           | Female            |
|                                | Mean ± SD      | Range ± 2SD       |
| LVEF (%)                       | 64±7           | 50–78             |
| EDV (mL)                       | 80±16          | 49–112            |
| ESV (mL)                       | 29±9           | 12–47             |
| EDV index (mL/m²)              | 47±9           | 30–64             |
| ESV index (mL/m²)              | 17±5           | 8–27              |

EDVI and ESVI are indices corrected by body surface area (m²). (Modified reproduction from Nakajima K\(^\text{44}\) with permission. Copyright (2010) by the Japanese Society of Nuclear Medicine. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/).

| Table 23. Standard Values of Diastolic Function With ECG-Gated Myocardial Perfusion SPECT (<60 Years Old) |
|---------------------------------|----------------|-------------------|
|                                | Mean ± SD      | Range ± 2SD       |
| PFR (/s)                       | 2.79±0.53      | 1.73–3.85         |
| 1/3FR mean (/s)                | 1.68±0.30      | 1.08–2.28         |
| TPF (ms)                       | 159±26         | 108–210           |
| TPF/RR interval                | 0.17±0.02      | 0.13–0.22         |

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time–activity curve for each pixel acquired by ECG-gated cardiac blood-pool scintigraphy, followed by displaying the phase and amplitude of the trigonometric function of the fundamental wave component as a functional image. Phase analysis enables display of time phase shifts during cardiac contraction as a map, and was therefore applied to assessment of local wall motion abnormalities or detection of the accessory pathway in patients with Wolff-Parkinson-White syndrome or biventricular pacing, etc.\(^3\) Subsequently, with the increased availability of ECG-gated myocardial perfusion SPECT, phase analysis has also been applied to analyze regional data in a similar manner using the regional time–activity curve (i.e., the curve for the change in counts during contraction and relaxation).\(^4\) When analyzing the timing of left ventricular contraction, it is usual to create a histogram showing the distribution of phases within the left ventricle and then calculate the standard deviation, the 95% bandwidth indicating the extent of phase spread, and the level of entropy (an index of disorder or randomness). There are several advantages to performing phase analysis of ECG-gated myocardial perfusion SPECT data. First, the original image is digital and therefore can be easily quantified. Second, ECG gating is a standard acquisition method for myocardial SPECT, so additional testing is unnecessary. Third, the images generally require little manual processing, leading to high reproducibility as long as the same software is used. Fourth, regional myocardial perfusion and phase abnormalities can be directly compared on the map.

The reference values for phase analysis depend on the algorithm being used. Accordingly, the reference values for different software programs are shown in Table 24.\(^5\) Interestingly, it was reported that diagnostic performance for detection of wall motion abnormalities does not vary among the software programs, even if their reference values are different.\(^6\) and phase analysis has been used to assess the association of abnormal wall motion with induced ischemia or multivessel disease, and for differentiation between ischemic and nonischemic heart failure.\(^7\) Moreover, it was reported that variation of phase values is an indicator of the efficacy of cardiac resynchronization therapy.\(^8\) and is useful for prognostic evaluation,\(^9\) although the actual usefulness of phase analysis has not yet been established.

### 8.1.6 Artifacts
Several factors have been identified as contributing to errors when functional analysis is performed with ECG-gated myocardial perfusion SPECT. When high accumulation persists in the liver or gallbladder, separation of these organs from the inferior wall of the left ventricle becomes difficult. To overcome this problem, imaging can be delayed until excretion from the liver has occurred, or in the case of accumulation in the gallbladder, an attempt can be made to wash out the accumulated tracer in the gallbladder by intake of milk or food.\(^3\) Extraction of the left ventricular contour is possible even when there is a myocardial perfusion defect, but a significant defect occupying a wide area can lead to errors. Currently available analytical software programs tend to overestimate LVEF while underestimating volumes in patients with a small left ventricular cavity, but this issue has been addressed in some programs by modifying the algorithm.\(^8\) Because ECG gating is used, the accuracy tends to decline when heart rate variability is large, such as when the patient has an arrhythmia during data acquisition. In addition, “noise” may affect the ECG triggers, and both the R and T waves may act as triggers in rare cases, so caution should be exercised to decide whether ECG gating is appropriate.\(^5\)

### 8.2 Evaluation of Left and Right Ventricular Function by Cardiac Blood-Pool Scintigraphy
Cardiac blood-pool scintigraphy shows good correlation with ventriculography for evaluation of left ventricular wall motion and is useful for assessing ischemic heart disease. However, its use has been decreasing in recent years. In patients receiving cardiotoxic anticancer drugs such as doxorubicin, cardiac blood-pool scintigraphy is useful both for initial assessment of cardiac function and for follow-up.\(^\text{72}\) Evaluation of patients receiving chemotherapy by cardiac blood-pool testing received a Class I recommendation in the ACC/AHA nuclear cardiology guidelines. Because quantification and reproducibility are both high, this test should also be considered in Japan when observation of cardiac function over time is required. In the future, evaluation is also expected to be done by 3-dimensional echocardiography and MRI, which are excellent methods for quantitative analysis.

Direct evaluation of right ventricular function by ECG-gated myocardial perfusion SPECT is impossible. Accordingly, the functional indices are calculated from images obtained in the left anterior oblique view by equilibrium ECG-gated cardiac blood-pool scintigraphy using

| Table 24. Standard Values of Phase Parameters With ECG-Gated Myocardial Perfusion SPECT Using Various Software Programs |
|-----------------|---------|---------|---------|---------|
|                | ECTb    | cREPO   | QGS     | HFV     |
| 95% band width (°) | Mean±SD | 29.4±9.3 | 40.3±11.6 | 21.9±8.6 | 19.9±9.1 |
|                 | Range±2SD | 11–49   | 17–64   | 5–39    | 2–38    |
| Phase SD (°)    | Mean±SD | 11.5±5.5 | 10.3±3.2 | 5.3±3.0 | 5.4±2.5 |
|                 | Range±2SD | 1–23    | 4–17    | 0–11    | 0–10    |
| Entropy (%)     | Mean±SD | 43.0±6.4 | 24.0±8.3 |
|                 | Range±2SD | 30–56   | 7–41    |

ECTb, Emory Cardiac Toolbox with SyncTool (Emory University/Syntermed, USA); cREPO, cardioREPO (FUJIFILM Toyama Chemical); QGS, Quantitative Gated SPECT (Cedars-Sinai Medical Center, USA); HFV, Heart Function View (Nihon Medi Physics). (Reproduced from Nakajima et al 2017,\(^3\) with permission. Copyright of authors, 2017. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/).
Tc-99m-labeled red blood cells. Because the left and right ventricles can be visualized simultaneously in this view, the right ventricular EF (RVEF) is calculated by setting a region of interest in the right ventricle. In recent years, a method has been developed that allows simultaneous analysis of right and left ventricular volumes and function by ECG-gated cardiac blood-pool SPECT. However, there are problems with its accuracy because the indices of right ventricular function vary depending on the setting of the valve plane, the acquisition angle, etc.

Recommenda-
tions and levels of evidence for evaluation of ventricular function with ECG-gated myocardial perfusion SPECT are shown in Table 25.

<table>
<thead>
<tr>
<th>Initial evaluation and follow-up of left ventricular function</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up of left ventricular function in patients with coronary heart disease</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>Prognostic evaluation in patients with coronary heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluation of left ventricular function in patients with heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluation of left ventricular diastolic function</td>
<td>IIb</td>
<td>C</td>
<td>C1</td>
<td>IVb</td>
</tr>
<tr>
<td>Evaluation of left ventricular dyssynchrony by phase analysis</td>
<td>IIb</td>
<td>C</td>
<td>C1</td>
<td>IVb</td>
</tr>
</tbody>
</table>

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

Table 26. Most Important Medications That May Affect Organ Uptake of MIBG

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Discontinuation (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Uptake inhibition</td>
<td>7–14</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Uptake inhibition</td>
<td>7–14</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Amitriptyline, imipramine, amoxapine, others</td>
<td>Uptake inhibition</td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>Amphetamine, ephedrine, dopamine, isoproterenol, salbutamol, others</td>
<td>Depletion of granules</td>
</tr>
<tr>
<td>Antihypertensive/ cardiovascular agents</td>
<td>Labetalol</td>
<td>Inhibition uptake and depletion</td>
</tr>
<tr>
<td></td>
<td>Reserpine</td>
<td>Depletion and transport inhibition</td>
</tr>
<tr>
<td></td>
<td>Guanethidine</td>
<td>Depletion and transport inhibition</td>
</tr>
<tr>
<td></td>
<td>Calcium-channel blockers</td>
<td>Increased uptake and retention</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Phenothiazines, thioxanthenes, butyrophenones, others</td>
<td>Uptake inhibition</td>
</tr>
</tbody>
</table>

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### 9. Myocardial Sympathetic Nervous Imaging

#### 9.2 Agents for Myocardial Sympathetic Nervous Imaging

Iodine-123 MIBG is a radiopharmaceutical used for evaluation of cardiac sympathetic nerve function. Iodine-123 has a half-life of 13 hours, and the effective gamma ray energy is 159 keV. Iodine-123 MIBG has a similar structure to norepinephrine and is taken up by sympathetic nerve terminals via a similar mechanism to that for norepinephrine. Because I-123 MIBG is not metabolized by catechol-O-methyltransferase or monoamine oxidase and does not bind to catecholamine receptors, imaging with this agent reflects the kinetics of neurotransmitter uptake, storage, and release by sympathetic nerve terminals.377–379 Evaluation of cardiac sympathetic nerve function is also possible with PET. A variety of PET tracers are available, including C-11 hydroxyephedrine, C-11 epinephrine, and F-18 fluorodopa, but clinical use is limited and these agents are not covered by health insurance.

#### 9.3 Pretreatment and Imaging

#### 9.3.1 Thyroid Block

Thyroid block is not essential because I-123 has a relatively short half-life and only emits gamma rays.380 Administration of potassium iodide or Lugol’s solution may be used to minimize exposure to the thyroid gland.
The heart-to-mediastinum ratio (H/M ratio) and the washout rate are calculated from planar images, and regional assessment is performed using SPECT images. The H/M ratio and washout rate have been shown to be significant prognostic factors in patients with heart failure, including those with coronary heart disease. According to studies from Japan, both the late H/M ratio and the washout rate were predictors of cardiac events in patients with heart failure and cardiac dysfunction, including patients who had coronary heart disease. An overseas study also showed that the late-phase H/M ratio was a predictor of cardiac events, and adding the H/M ratio to models predicting cardiac events improved their accuracy.

In those reports, the cutoff value for the H/M ratio was 2.0 when converted to the ratio for a standard medium-energy collimator. Moreover, it has been reported that appropriate ICD therapy for ventricular tachyarrhythmias is frequent among the studies for heart failure, the proportion of chronic coronary heart disease in study subjects varied depending on the report. COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

### 9.3.2 Medications Before Testing
Given the diverse range of drugs that may potentially influence cardiac I-123 MIBG uptake, it is advisable to discontinue all applicable drugs before testing, including tricyclic antidepressants and antipsychotics (Table 26).

### 9.3.3 Imaging Technique
A dose of 111 MBq of I-123 MIBG is injected intravenously under resting conditions. Imaging should be performed twice: that is, 15–30 min (early images) and 180–240 min (late images) after intravenous injection. Both planar and SPECT images are collected. Attention must be paid to the collimator used during imaging. Because measured values vary between low-energy collimators and medium-energy collimators, correction with a conversion factor is necessary according to the type of collimator.

### 9.3.4 Evaluation Method
The heart-to-mediastinum ratio (H/M ratio) and the washout rate are calculated from planar images, and regional assessment is performed using SPECT images. The H/M ratio and washout rate are calculated by setting regions of interest on the entire heart and the upper mediastinum in a planar image (Figure 7). Formulas for calculating the H/M ratio and washout rate are as follows:

\[
\text{H/M ratio} = \frac{\text{cardiac count}}{\text{mediastinal count}}
\]

\[
\text{Washout rate (\%)} = \frac{100}{(\text{early image} - \text{late image}) / (\text{early image})}
\]

The reference value for the H/M ratio is 2.2–4.0 on early images and 2.2–4.4 on late images when a standard medium-energy collimator is used. The reference value for the washout rate is 6–30% with correction for physiological decay of I-123.

### 9.4 Clinical Significance
The most important indication for I-123 MIBG imaging is assessing the prognosis of patients with heart diseases, and it is useful for risk stratification in patients with heart failure, cardiomyopathy, or ventricular tachyarrhythmias.

Myocardial sympathetic nerve function is impaired in patients with coronary heart disease, and I-123 MIBG accumulation is decreased in regions affected by ischemia or scarring. Myocardial perfusion scintigraphy is more useful for diagnosis of coronary heart disease, and evaluation of sympathetic nerve dysfunction is only complementary to anatomical assessment of coronary artery pathology. On the other hand, I-123 MIBG imaging is considered to be useful for risk stratification in patients who have chronic coronary heart disease with heart failure (ischemic heart failure) or coronary heart disease associated with ventricular tachyarrhythmias. Such uses are described below.

### 9.4.1 Prognostic Evaluation (Table 27)
The H/M ratio and washout rate have been shown to be significant prognostic factors in patients with heart failure, including those with coronary heart disease. According to studies from Japan, both the late H/M ratio and the washout rate were predictors of cardiac events in patients with heart failure and cardiac dysfunction, including patients who had coronary heart disease. An overseas study also showed that the late-phase H/M ratio was a predictor of cardiac events, and adding the H/M ratio to models predicting cardiac events improved their accuracy.

In those reports, the cutoff value for the H/M ratio was 2.0 when converted to the ratio for a standard medium-energy collimator. Moreover, it has been reported that appropriate ICD therapy for ventricular tachyarrhythmias is frequent when local accumulation of I-123 MIBG is substantially decreased in the late phase, and this finding may be useful for predicting lethal arrhythmias.

### 9.4.2 Diagnosis
Cardiac sympathetic nerve imaging has a limited role in the diagnosis of chronic coronary heart disease, and evaluating cardiac sympathetic nerve function alone is not sufficient for assessment of heart disease. Instead, assessment should be performed by integrating data from various modalities, including morphological evaluation by coronary angiography or coronary CT, detection of ischemia by methods such as stress myocardial perfusion scintigraphy, and the assessment of myocardial viability by using 18F-FDG-PET and LGE MRI.

Accumulation of I-123 MIBG is reduced in myocardial regions affected by infarction or ischemia. In patients with

| Table 27. Recommendations and Levels of Evidence for Prognostic Evaluation by Myocardial Sympathetic Nervous Imaging for Heart Failure Due to Chronic Coronary Heart Disease (Ischemic Heart Failure) |
|-----------------|-----|-----|-----|-----|
| Prognostic evaluation for ischemic heart failure | COR | LOE | GOR (MINDS) | LOE (MINDS) |
| IIA | C | B | IVb |

Among the studies for heart failure, the proportion of chronic coronary heart disease in study subjects varied depending on the report. COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.
Table 28. Summary of Myocardial Sympathetic Nervous Imaging

<table>
<thead>
<tr>
<th>I-123 MIBG</th>
<th>Application</th>
<th>Evaluation of cardiac sympathetic nervous function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Half-life</td>
<td>13 hours</td>
</tr>
<tr>
<td></td>
<td>Effective gamma ray energy</td>
<td>159 keV</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Similar to norepinephrine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pretreatment and imaging</th>
<th>Pretreatment</th>
<th>Not essential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging technique</td>
<td>Dose</td>
<td>111 MBq</td>
</tr>
<tr>
<td></td>
<td>Imaging</td>
<td>Early: 15–30 min after intravenous injection</td>
</tr>
<tr>
<td></td>
<td>Late: 180–240 min after intravenous injection</td>
<td>Planar and SPET images</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evaluation method</th>
<th>Heart-to-mediastinum ratio (H/M ratio)</th>
<th>Cardiac count/mediastinal count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washout rate (%) (WR)</td>
<td>(Cardiac count [early image] – mediastinal count [early image]) – (Cardiac count [late image] – mediastinal count [late image])</td>
<td>( \frac{\text{Cardiac count [early image] – mediastinal count [early image]}}{\text{Cardiac count [early image] – mediastinal count [late image]}} \times 100 )</td>
</tr>
<tr>
<td>Reference value</td>
<td>H/M ratio: 2.2–4.4</td>
<td>WR: 6–30% (with correction for physiological decay of I-123)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical significance</th>
<th>Prognostic evaluation</th>
<th>Heart failure, ventricular tachyarrhythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diagnosis</td>
<td>Limited role in the diagnosis of chronic coronary heart disease</td>
</tr>
<tr>
<td></td>
<td>Evaluation of treatment effect</td>
<td>Pharmacotherapy, cardiac resynchronization therapy</td>
</tr>
</tbody>
</table>

myocardial infarction and angina pectoris, the MIBG defect is often more extensive than the zone of decreased blood flow, and areas of mismatch with blood flow may reflect myocardium at risk. Previous reports have shown that I-123 MIBG has the same performance for diagnosis of coronary heart disease as exercise Tl-201 scintigraphy. However, accumulation in the inferior wall of the left ventricle decreases with age, leading to an increase in false-positive results, and evaluation of the inferior wall is often difficult due to artifacts.

Because accumulation of I-123 BMIPP or I-123-9-MPA is thus difficult to obtain good images and unsuitable for clinical use. This method does not directly assess sensitively detect ischemic injury by assessing myocardial fatty acid metabolism. PET can be used to evaluate fatty acid metabolism by assessing the \( \beta \)-oxidation of C-11-labeled palmitic acid (which is used in vivo). However, metabolism of this straight-chain fatty acid is rapid and it is thus difficult to obtain good images and unsuitable for clinical use. On the other hand, iodine (I-123 BMIPP and I-123-iodophenyl-9-methyl-pentadecanoic acid (I-123-9-MPA) are long-chain fatty acids with side chains in which a methyl group has been introduced at the position of palmitic acid. These agents are not susceptible to \( \beta \)-oxidation, show good myocardial retention, and can be easily detected with a conventional gamma camera, allowing this imaging method to capture energy metabolism and fatty acid metabolism by cardiomyocytes at the molecular level in daily clinical practice. This method does not directly assess \( \beta \)-oxidation, but reflects the uptake of long-chain fatty acids by cardiomyocytes via specific transporters, as well as their intracellular transport and storage (triglyceride pool). Because accumulation of I-123 BMIPP or I-123-9-MPA depends on the myocardial ATP concentration, it indirectly reflects myocardial fatty acid metabolism. This section describes myocardial I-123 BMIPP imaging, which is widely used in routine practice and for which relevant clinical data have been obtained.

### 10. Myocardial Fatty Acid Imaging

#### 10.1 Myocardial Energy Metabolism

The heart constantly requires an abundant source of energy (ATP) to function. Under aerobic conditions, more than 60% of the myocardial energy requirement is obtained from long-chain fatty acids, with the remainder being mainly derived from glucose and only a few percent from amino acids and lactic acid (fatty acid–glucose cycle). However, \( \beta \)-oxidation of fatty acids requires an abundant supply of oxygen and is easily affected by impaired myocardial blood flow (ischemia). This makes it possible to indirectly reflect the uptake of long-chain fatty acids by cardiomyocytes via specific transporters, as well as their intracellular transport and storage (triglyceride pool). Because accumulation of I-123 BMIPP or I-123-9-MPA depends on the myocardial ATP concentration, it indirectly reflects myocardial fatty acid metabolism. This section describes myocardial I-123 BMIPP imaging, which is widely used in routine practice and for which relevant clinical data have been obtained.

#### 10.2 Myocardial I-123 BMIPP Imaging

##### 10.2.1 Data Collection

A low blood glucose level is preferable to increase the uptake of fatty acids by the myocardium. Therefore, 111–148 MBq of I-123 BMIPP (3–4 mCi) is administered intra-
accumulation in the inferior wall (artifact) due to absorption of its higher energy, and there is a smaller decrease in this agent. I-123 shows less attenuation than Tl-201 because BMIPP is uniform because of good accumulation of resolution semiconductor camera is required. Blood flow imaging is difficult with a conventional gamma clides by using I-123 BMIPP and Tc-99 m for myocardial however, simultaneous acquisition of data on 2 radionuclides (primarily down-scatter by I-123 has an effect on comparison of myocardial blood flow and fatty acid metabolism in the same tomographic image. Although interference occurs during simultaneous acquisition of data on 2 radionuclides (primarily down-scatter by I-123 has an effect on Tl-201 images), the effect is smaller when accumulation of I-123 BMIPP is abnormal. Therefore, it becomes easier to accurately evaluate metabolic dysfunction in ischemic myocardium and to identify the presence/absence of myocardial flow-fatty acid metabolism mismatch (described later). However, simultaneous accumulation of data on 2 radionuclides by using I-123 BMIPP and Tc-99 m for myocardial blood flow imaging is difficult with a conventional gamma camera because the energy peaks are too close, and a high-resolution semiconductor camera is required.

10.2.2 Analysis (Visual and Semiquantitative Evaluation)
Visual assessment of SPECT images (evaluation of the site, extent, and severity of decreased accumulation) and semiquantitative visual evaluation are generally performed in a similar manner to the evaluation of myocardial perfusion SPECT imaging, based on 17 segments and a 5-point score. A 2-dimensional polar coordinate display method using concentrically arranged short-axis tomographic images is also widely used because it facilitates evaluation of abnormal accumulation and enables quantitative assessment. Recent advances in image analysis software have made it easier to automate the scoring of the 17 segments and to quantify abnormal accumulation on the 2D polar coordinate display. Such software has also been applied for prognostic evaluation and for quantification of blood flow–metabolism mismatch.

When the result is normal, myocardial distribution of I-123 BMIPP is uniform because of good accumulation of this agent. I-123 shows less attenuation than Tl-201 because of its higher energy, and there is a smaller decrease in accumulation in the inferior wall (artifact) due to absorption by the diaphragm with I-123 than with TI-201.413 Myocardial I-123 BMIPP imaging with an early (20–30 min after administration) and late (3–4 hours after administration) imaging protocol has been reported, as well as methods for evaluating the myocardial washout rate. However, the clinical significance of these methods has not been established in patients with coronary heart disease.

Table 29. Correlations Between Myocardial Blood Flow (MBF) and Metabolism of Glucose and Long-Chain Fatty Acids (LCFA) in Normal Myocardium and in Various Pathophysiologies of Myocardial Ischemia

<table>
<thead>
<tr>
<th>Condition</th>
<th>MBF at rest (myocardial viability)</th>
<th>MBF at stress</th>
<th>Regional wall motion at rest</th>
<th>Myocardial energy metabolism in the fasting condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal myocardium</td>
<td>Normal</td>
<td>Increased</td>
<td>Normal</td>
<td>BMIPP (LCFA) accumulation</td>
</tr>
<tr>
<td>Ischemic myocardium (reversible ischemia)</td>
<td>Normal to mild decrease</td>
<td>Increased</td>
<td>Decreased (reversible)</td>
<td>Increased (compensatory)</td>
</tr>
<tr>
<td>Stunned myocardium (Alleviation of acute ischemia)</td>
<td>Mild-to-moderate decrease</td>
<td>Insufficient increase (ischemia)</td>
<td>Decreased (reversible)</td>
<td>Increased (compensatory)</td>
</tr>
<tr>
<td>Hibernating myocardium (persistent ischemia) and Ischemia-induced failing myocardium</td>
<td>Severe decrease</td>
<td>Severe decrease</td>
<td>Severe decrease (irreversible)</td>
<td>Severe decrease (irreversible)</td>
</tr>
</tbody>
</table>

10.3 Mechanism and Clinical Significance of Abnormal Myocardial I-123 BMIPP Accumulation
As described above, abnormally reduced myocardial I-123 BMIPP accumulation theoretically reflects one or more of the following abnormalities: decreased uptake of long-chain fatty acids by a specific transporter (CD36) in the cardiomyocyte membrane, abnormal handling of long-chain fatty acids by a specific intracellular transporter (H-FABP) in cardiomyocytes, decreased myocardial lipid storage (triglyceride pool), impaired mitochondrial transport (carnitine shuttle), and decreased mitochondrial β-oxidation with a resultant decrease in the myocardial ATP concentration.

The most important factor in impaired myocardial fatty acid metabolism is reduced myocardial blood flow that causes myocardial ischemia. When myocardial ischemia occurs and leads to oxygen deficiency, β-oxidation of fatty acids in the mitochondria (which requires abundant oxygen) is rapidly inhibited and ATP production is reduced. Because ATP depletion means that fatty acids are not activated to form acyl-CoA in cardiomyocytes (decreased fatty acid consumption), the myocardial fatty acid storage pool shrinks and fatty acid transport to the mitochondria is inhibited. These ischemic derangements of myocardial fatty acid metabolism result in abnormal myocardial accumulation of I-123 BMIPP. Abnormal myocardial fatty acid metabolism often persists after restoration of coronary blood flow and alleviation of myocardial ischemia by acute coronary revascularization, and this phenomenon is known as ischemic memory.414–416 The existence of ischemic memory greatly improves the accuracy of detecting myocardial ischemia by I-123 BMIPP imaging, and ischemic memory occurs because recovery of myocardial fatty
acid β-oxidation is delayed, unlike recovery of glucose metabolism (Table 29).

During this period, ATP production by glucose metabolism is insufficient to maintain myocardial viability and it takes time to normalize cardiomyocyte function (contractility). Based on ischemic memory, hibernating myocardium and stunned myocardium caused by myocardial ischemia can be detected by myocardial I-123 BMIPP imaging. Table 29 summarizes the relationships among myocardial blood flow, contractility (wall motion), myocardial fatty acid metabolism (I-123 BMIPP accumulation), and myocardial glucose metabolism (18F-FDG accumulation) in healthy myocardium, ischemic myocardium, myocardium after alleviation of acute ischemia (stunned myocardium), chronically ischemic myocardium (hibernating myocardium), and infarcted (necrotic) myocardium. By comparing myocardial blood flow, contractility (wall motion), and myocardial fatty acid metabolism, the detailed pathophysiology of ischemic myocardial injury can be understood, helping to determine the effect of treatment and assess the prognosis. This imaging technique is safe and can be performed with a conventional gamma camera. It is a noninvasive resting examination with no effect on hepatorenal or cardiac function, and is unaffected by the presence of comorbidities. Unlike 18F-FDG imaging, BMIPP imaging is also able to diagnose coronary heart disease in patients with diabetes or hyperlipidemia, as in nondiabetic patients, because there is only limited influence of substrates in the blood (glucose, cholesterol, fatty acids, insulin, etc.).

### 10.4 Suspected or Confirmed Stable Chronic Coronary Heart Disease

The effect of ischemia on myocardial fatty acid metabolism depends on the severity of the myocardial ischemia. Hence, the diagnostic accuracy of myocardial I-123 BMIPP imaging is higher for acute and severe ischemia and lower for chronic and mild ischemia. In patients with stable chronic coronary heart disease, myocardial ischemia is induced by exercise or other stresses, and can be persistent, often being painless and occult. Moreover, recovery of myocardial fatty acid metabolism is delayed after alleviation of ischemia (improvement of myocardial blood flow). Accordingly, myocardial I-123 BMIPP imaging at rest can detect ischemia, determine its severity, and investigate the presence or absence of recent ischemic episodes, and detection of ischemic memory is of diagnostic significance in patients with stable chronic coronary heart disease.

### 10.4.1 Diagnostic Significance

A major advantage of myocardial I-123 BMIPP imaging is that it is a resting examination. Therefore, it is useful when it is difficult for the patient to perform exercise or pharmacological stress testing (e.g., contraindications to drugs [bronchial asthma, atrioventricular block, severe bradycardia, hypotension, etc.], use of antianginal drugs such as nitrates and β-blockers, and suspected coronary heart disease when ACS cannot be excluded). The presence of a certain level of chronic myocardial ischemia is required for the onset of myocardial fatty acid metabolism disorder. It has been reported that the diagnostic accuracy of I-123 BMIPP imaging for stable chronic coronary heart disease is almost equivalent (concordance of ~90%) to that of stress myocardial perfusion imaging, which has already been established as useful. Although the diagnostic accuracy for reversible ischemia in routine clinical practice is not necessarily high (50–60%), it is relatively consistent with resting wall motion abnormalities (70%). Thus, the diagnostic accuracy of I-123 BMIPP imaging is clearly superior to that of resting myocardial perfusion imaging.

In the absence of a history of myocardial infarction, abnormal BMIPP accumulation may be seen despite normal myocardial perfusion (i.e., mismatch occurs between myocardial blood flow and BMIPP accumulation). When stress myocardial perfusion imaging is negative (false-negative result, multivessel disease, heart failure, insufficient loading, etc.), if decreased myocardial BMIPP accumulation is consistent with a coronary artery territory, the possibility of coronary heart disease and a prior ischemic episode is high. Thus, multiple sites of abnormal BMIPP accumulation suggest the possibility of multivessel disease.

### 10.4.2 Vasospastic Angina

Vasospastic angina may be induced by exercise, exposure to cold, or other stress, and is often associated with stable or chronic coronary heart disease. Conventional stress testing with exercise loading or vasodilators does not have a high diagnostic accuracy for vasospastic angina. In addition, it is not easy to detect spontaneous attacks leading to myocardial ischemia, because severe attacks often occur at night or in the early morning. However, this disease can give rise to severe ischemia associated with ST elevation that persists for a relatively long time, which means myocardial I-123 BMIPP imaging can be used to diagnose coronary vasospasm with a high sensitivity and specificity (both ~70–90%), even after the offset of vasospasm, and is also useful for determining the effect of treatment with calcium antagonists or other agents. When a test result is abnormal, coronary angiography or coronary CT is subsequently required to assess coronary artery morphology. Because abnormal myocardial fatty acid metabolism is a reflection of ischemia, the diagnostic accuracy of this test is influenced by the severity of ischemia and the time until recovery from ischemia, so caution should be exercised regarding negative results.

### 10.4.3 Hibernating Myocardium

Hibernating myocardium is affected by chronic, persistent ischemia and is associated with abnormal regional wall motion. In this condition, myocardial contractility is suppressed (hibernation) because of severe persistent ischemia, even in the absence of myocardial necrosis, and its diagnosis is important for determining the indications for procedures such as coronary revascularization. If myocardium is hibernating, its viability is maintained and contractility can be restored within several months after alleviation of chronic myocardial ischemia. However, whether or not hibernating myocardium affected by chronic ischemia is actually viable usually cannot be judged from assessment of regional wall motion alone, although judgment is possible if reversible myocardial ischemia is induced. In contrast to necrotic myocardium, hibernating myocardium appears almost normal on resting myocardial imaging (indicating its viability), while showing impaired fatty acid metabolism and increased glucose metabolism, as well as reduced accumulation of I-123 BMIPP (indicating ischemic injury). Therefore, mismatch between these findings can be diagnosed by imaging at rest. The severity and extent of abnormal myocardial I-123 BMIPP accumulation...
correlate with the decrease in wall motion and LVEF. Because wall motion and LVEF show improvement within several months after coronary revascularization, I-123 BMIPP imaging is useful for both diagnosing hibernating myocardium and predicting its recovery.420–423

10.4.4 Prognostic Evaluation
Because abnormal myocardial I-123 BMIPP accumulation also reflects prior ischemic events, chronic persistent abnormal accumulation is related to prognosis.434–438 In patients with coronary heart disease, including those with ACS or chest pain, the severity of reversible abnormal myocardial blood flow, a low LVEF, and diabetes mellitus are conventionally considered to be significant prognostic indicators. The severity of abnormal myocardial I-123 BMIPP accumulation and mismatch of I-123 BMIPP accumulation with blood flow are also significantly associated with future cardiac events, and these indicators can contribute to more accurate prediction of the prognosis.438

In patients without myocardial infarction, the prognosis is good if myocardial I-123 BMIPP imaging is normal or slightly abnormal (i.e., this test has a high negative predictive value).439 Thus, risk stratification (differentiation between low- and high-risk patients) and prognostic evaluation can be performed for coronary heart disease by using myocardial I-123 BMIPP imaging, based on the fact that inhibition of myocardial fatty acid metabolism is a sensitive response to myocardial ischemia and reflects both infarcted myocardium and ischemic myocardium at risk of further damage in future cardiac events.

10.4.5 Ischemic Heart Failure and Ischemic Cardiomyopathy
Patients with chronic coronary heart disease, especially those with heart failure, are increasing in number, although they may not have typical symptoms of stable chronic coronary heart disease. Caution should be especially exercised with regard to elderly patients and those with diabetes or renal failure. If obvious organic disease (hypertensive cardiac hypertrophy, valvular disease, congenital heart disease, cardiomyopathy, etc.) is ruled out, then it is important to identify heart failure caused by coronary heart disease (ischemic heart failure and ischemic cardiomyopathy). Coronary angiography is required for a definitive diagnosis, but it is often not easy to perform because of the poor general condition of the patient, including renal dysfunction. In such patients, myocardial I-123 BMIPP imaging is a relatively easy and safe resting test. A defect of I-123 BMIPP accumulation corresponding to a specific coronary artery territory is strongly suggestive of coronary heart disease.

Simultaneously performing myocardial perfusion imaging (i.e., simultaneous imaging with 2 radionuclides) can distinguish between heart failure due to left ventricular remodeling after myocardial infarction, in which myocardial viability cannot be expected (defect of I-123 BMIPP accumulation and myocardial perfusion defect at rest), and heart failure due to coronary heart disease where revascularization is expected to be effective. In the latter case, I-123 BMIPP accumulation is abnormal even though resting myocardial perfusion is maintained to some extent, indicating viable myocardium (myocardial blood flow–metabolism mismatch).440 In patients with idiopathic dilated cardiomyopathy, which is often difficult to differentiate from ischemic cardiomyopathy, it is known that cardio-

10.4.6 Diagnosis and Prognostic Evaluation in Patients With Diabetes or CKD and Dialysis Patients
Patients with diabetes or CKD, as well as patients on dialysis, often have concomitant hypertension and a high risk of coronary heart disease leading to cardiovascular events such as heart failure and sudden death. However, diagnosis tends to be delayed because of a lack of symptoms and difficulty in performing tests for coronary heart disease using contrast medium. Combined with the influence of contrast-induced renal damage, delayed diagnosis worsens the prognosis of such patients. Although stress myocardial perfusion imaging is generally useful in these high-risk patients, myocardial I-123 BMIPP imaging can be an alternative when performing a stress test is difficult because of the patient’s general condition and blood pressure. Several investigations, including a multicenter Japanese study (B-SAFE study), have identified the usefulness of I-123 BMIPP imaging for diagnosis of asymptomatic coronary heart disease in patients with diabetes or renal dysfunction,443,444 as well as for predicting cardiovascular events and the prognosis.445–447 Evaluation of treatment,448 and assessing the risk of sudden death in patients on chronic dialysis449 (Table 30).

11. Positron Emission Tomography (PET)

11.1 Significance in the Diagnosis of Chronic Coronary Heart Disease
When a pair of high-energy gamma rays (511keV) are

Table 30. Recommendations and Levels of Evidence for Myocardial BMIPP Imaging in Various Pathophysiologies of Myocardial Ischemia for the Diagnosis of Chronic Coronary Heart Disease

<table>
<thead>
<tr>
<th>Diagnostic target</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial ischemia</td>
<td>IIa</td>
<td>C</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>Hibernating myocardium</td>
<td>IIb</td>
<td>C</td>
<td>B</td>
<td>IVb</td>
</tr>
<tr>
<td>Vasospastic angina</td>
<td>IIa</td>
<td>C</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>Myocardial ischemia in dialysis patients</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>III</td>
</tr>
<tr>
<td>Risk &amp; prognosis assessment in dialysis patients</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>III</td>
</tr>
<tr>
<td>Risk &amp; prognosis assessment</td>
<td>IIa</td>
<td>B</td>
<td>B</td>
<td>IVa</td>
</tr>
</tbody>
</table>

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.
emitted at 180 degrees from opposite directions as a result of the annihilation of positron-emitting radionuclides, paired and opposed detectors obtain positional information by localizing their source along a straight line of coincidence. With these emission mechanisms and scan techniques, PET has a greater sensitivity of gamma ray count per unit time and higher spatial resolution than SPECT, and CT attenuation correction is generally performed and has achieved better image quality as hybrid PET/CT scanners become popular.

A cardiovascular PET scan for diagnosis of myocardial viability using \(^{18}\text{F-FDG}\) has only been covered by health insurance since 2002. Since 2012 it can be used for diagnosis of inflammation in cardiac sarcoidosis using FDG and evaluation of myocardial perfusion using \(^{13}\text{N-ammonia}\), and since 2018 for diagnosis of large vessel vasculitis using FDG. \(^{18}\text{F-FDG}\) has a relatively long half-life of about 110 min and can be supplied by on-site preparation using a small cyclotron or purchased from manufacturers. In contrast, \(^{13}\text{N-ammonia}\) used for myocardial perfusion PET has a short half-life of 10 min and on-site preparation is required.

<table>
<thead>
<tr>
<th>11.1.1 Assessment of Myocardial Viability Using (^{18}\text{F-FDG}) (Table 31)</th>
</tr>
</thead>
</table>
| \(^{18}\text{F-FDG}\) is a glucose analog in which the hydroxyl group at the C-2 position of glucose is substituted by F-18. Like glucose, \(^{18}\text{F-FDG}\) is taken up into cells via a glucose transporter in the plasma membrane and phosphorylated by hexokinase. Unlike glucose, \(^{18}\text{F-FDG}\) is retained in the cell without being metabolized.\(^{452}\) Because of high uptake by cells with active glucose metabolism, \(^{18}\text{F-FDG}\) imaging is mainly used for the diagnosis of malignant tumors. However, cardiomyocytes also show substantial accumulation of \(^{18}\text{F-FDG}\).\(^{453,454}\) In Japan, diagnosis of myocardial viability by \(^{18}\text{F-FDG}\) imaging in patients with poor left ventricular function is covered by health insurance.

In patients with OMI ventricular dysfunction and stenosis of the coronary artery supplying the infarcted region, viable myocardium is assumed to be present in this region if the wall motion and LVEF are improved by recanalization (reperfusion) therapy.\(^{432,455}\) By determining whether viable myocardium exists in the infarct zone before recanalization (reperfusion) therapy, its effect can be predicted and unnecessary invasive treatment can be avoided.\(^{459}\) In patients with residual viable myocardium, the incidence of cardiac events is lower after recanalization (reperfusion) therapy than after conservative treatment with drugs.\(^{229,306,456}\) Determination of myocardial viability using FDG-PET in patients with heart failure due to coronary heart disease is only covered by health insurance if it is difficult to judge using myocardial perfusion SPECT. That is, patients with poor left ventricular function who are judged to have no viable myocardium are only eligible for FDG-PET imaging. In actual practice, evaluation of myocardial viability by FDG-PET is often performed in patients without viable myocardium on perfusion imaging who show insufficient improvement of left ventricular function with medication, presumably in anticipation of a therapeutic effect of recanalization (reperfusion) therapy.

The myocardium primarily obtains energy from aerobic metabolism of fatty acids and anaerobic glycolysis via the TCA cycle. However, energy can also be supplied by a variety of other substrates, such as lactate, ketone bodies, and amino acids, and the source is determined by a range of factors, including food intake, hunger, exercise, myocardial ischemia, and cardiac dysfunction.\(^{457}\) Tests for diagnosis of myocardial viability are performed in the presence of high glucose uptake in order to promote uptake of \(^{18}\text{F-FDG}\) by viable cardiomyocytes. If the patient does not have diabetes, he/she fasts for 6 hours or longer and then orally ingests 50–100 g of glucose at 30 min before \(^{18}\text{F-FDG}\) administration. In patients with diabetes mellitus, continuous intravenous infusion of insulin and glucose is performed to maintain a constant glucose level (glucose–insulin clamp)\(^{458}\) or oral glucose loading is followed by administration of 1–5 units of rapid-acting insulin, depending on the blood glucose level.\(^{459}\)

\(^{18}\text{F-FDG}\) is administered at a dose of 185–444 MBq (3–7 MBq/kg), depending on the scanner specifications, but by using 3-dimensional acquisition, which has higher count sensitivity than 2-dimensional acquisition, the \(^{18}\text{F-FDG}\) dose can be reduced to 111–259 MBq (2–5 MBq/kg).\(^{460}\) From at least 45 min after \(^{18}\text{F-FDG}\) administration (usually 60–90 min), a 1-bed scan for cardiac imaging is carried out. The longer the interval from administration, the better the contrast of myocardium-to-the-background is achieved as \(^{18}\text{F-FDG}\) uptake in the blood pool decreases. Although the contrast is better at ≥90 min after \(^{18}\text{F-FDG}\) administration, the count activity decreases.

Reconstructed images of the left ventricular myocardium are obtained in 3 views (short-axis, vertical long-axis, and horizontal long-axis), and interpretation is usually performed by comparison with myocardial perfusion SPECT or PET imaging. With myocardial perfusion SPECT images at rest, myocardial viability is considered if myocardial uptake in the infarct area is ≥50\% (for TI) or ≥60\% (for Tc) in comparison with normal area. With FDG-PET alone, the presence of viable myocardium can be assumed if ≥50\% uptake is seen in the infarct area.\(^{461}\) Myocardial viability is also considered in the infarct area if \(^{18}\text{F-FDG}\) uptake is greater than that observed by resting perfusion imaging.

### Table 31. Recommendations and Levels of Evidence for Assessment of Myocardial Viability Using FDG-PET for the Diagnosis of Chronic Coronary Heart Disease

<table>
<thead>
<tr>
<th>Evaluation of CAD patients with left ventricular dysfunction</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>B</td>
<td>B</td>
<td>III</td>
<td></td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; COR, class of recommendation; GOR, grade of recommendation; IHD, ischemic heart disease; LOE, level of evidence.
Even if perfusion imaging shows myocardial uptake ≤50% in the infarct area, greater ¹⁸F-FDG uptake indicates myocardial viability. A meta-analysis showed that FDG-PET has sensitivity of 91% and specificity of 61% for diagnosis of myocardial viability, with its sensitivity being higher than that of myocardial perfusion imaging or dobutamine stress echocardiography. Therefore, FDG-PET is unlikely to underestimate residual viable myocardium compared with other modalities, but consideration should be given to revascularization not always achieving improvement of left ventricular function even when viability is expected from the FDG-PET results. It has also been reported that FDG-PET can distinguish between ischemic and nonischemic cardiac dysfunction with a sensitivity of 100% and specificity of 80%. A meta-analysis demonstrated good diagnostic performance of myocardial perfusion PET by visual assessment for coronary stenosis detected by invasive coronary angiography as the gold standard, with sensitivity of 90–93% and specificity 81–88%, which were superior to those of SPECT. It has been reported that normal PET results promise low probability of coronary stenosis and extremely low incidence of cardiac events with its high negative predictive value. Reports also indicate that the severity of ischemia or infarction from semiquantitative visual analysis of myocardial perfusion PET correlates with the prognosis. The LVEF obtained by ECG-gated analysis has been reported as an independent prognostic factor. The CFR obtained by quantitative PET analysis is a prognostic indicator independent of a visual assessment, and a combination of these 2 parameters allows accurate prognostic risk stratification. In the daily clinical setting, myocardial perfusion PET is useful for patients with multivessel disease in whom diagnosis of ischemia by myocardial perfusion SPECT is difficult and often underestimated, especially those with left main trunk disease and triple-vessel disease, which is easily generated by generators and covered by health insurance in the USA, has been used in most of the reported evidence about myocardial perfusion PET, but the number of reports on ¹⁳N-ammonia N-13 is increasing.

Myocardial perfusion PET is associated with less radiation exposure than SPECT and shows better diagnostic performance. However, ¹⁳N-ammonia requires on-site preparation using a small cyclotron, so it can only be performed at a limited number of centers at present. Myocardial perfusion PET could be performed at many centers with PET scanners if a perfusion tracer with F-18, which has a long half-life and can be delivered by manufacturers, is approved for use in Japan in the future. For visual analysis, image reconstruction is performed using 5–15 min of data collected between 90 s and 3 min after administration, because most of the tracer is taken up into the myocardium by 90 s after administration. A study comparing several software programs for quantitative analysis of myocardial blood flow found high reproducibility of quantitative analysis, with little difference between different software programs.

### Table 32. Recommendations and Levels of Evidence for Ammonia Myocardial Perfusion PET

<table>
<thead>
<tr>
<th>Diagnosis of CAD in patients with intermediate to high pretest probability</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk stratification and prognostic analysis based on ischemic and infarct volume</td>
<td>I</td>
<td>B</td>
<td>A</td>
<td>IVa</td>
</tr>
<tr>
<td>Risk stratification and prognostic analysis using quantitative myocardial perfusion kinetic analysis in conjunction with visual analysis</td>
<td>I</td>
<td>B</td>
<td>A</td>
<td>IVa</td>
</tr>
<tr>
<td>Risk stratification and prognostic analysis using ECG-gated left ventricular function analysis in addition to visual analysis</td>
<td>IIa</td>
<td>B</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>Detection of left main disease or severe multivessel disease by quantitative myocardial perfusion kinetic analysis</td>
<td>IIa</td>
<td>C</td>
<td>B</td>
<td>IVb</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.
high myocardial extraction ratio of 94%,\(^4\) and is rapidly taken up from the blood by cardiomyocytes, showing good retention. Compared with ammonia, \(^{13}F\)-fluorpiridaz achieves higher myocardial contrast vs. the blood pool, lungs, and liver, which is more suitable for visual assessment,\(^4\) and it is also excellent for quantitative analysis of blood flow.\(^4\)

**12. Coronary CT Angiography (CCTA)**

The use of CCTA, a technique of cardiac CT, has been rapidly and widely spreading in cardiovascular medicine. To maximize the usefulness of cardiac CT, this section will first provide the basics of cardiac CT, including its characteristics, principles of data acquisition, and management of radiation exposure. Next, it will also outline the evaluation and reporting systems used in the assessment of CCTA and cardiac CT. Finally, this section will highlight the utilization of both the morphological coronary artery assessment (stenosis and plaque) and newly developed functional assessment (myocardial perfusion and coronary blood flow) assessments through cardiac CT in the diagnostic algorithm for chronic coronary heart disease.

Given the technical progress in MDCT, CCTA has rapidly become a reliable diagnostic tool for CAD in clinical practice.\(^4\) In fact, invasive coronary angiography has long been considered the standard diagnostic technique, whereas CCTA represents an increasingly important tool for noninvasive imaging and assessment of ischemic heart disease. It is comparable to other techniques such as stress ECG, stress myocardial perfusion imaging (SPECT, MRI, and PET) and stress echocardiography.\(^2\) In addition to morphological assessment of coronary artery stenosis and plaque (Figure 8) by CCTA, cardiac CT enables functional assessment of myocardial perfusion and coronary blood flow through recently developed various imaging and analytical methodologies.\(^2,4,49\) However, CCTA may not always be sufficient to evaluate patients with arrhythmia or massive coronary artery calcification. In clinical practice, it is also required to have adequate knowledge of the side effects of contrast media and radiation exposure. The following section introduces the principles behind cardiac CT, image data acquisition and the related precautions, as well as the basic evaluation methods. Finally, it describes the new imaging technologies and methods of analysis.

**12.1 Advances in Cardiac MDCT**

The recent MDCT technology features (1) a wider detector, (2) high spatial resolution, (3) high temporal resolution, and (4) iterative reconstruction as well as advances in the associated technologies. All these factors contribute to improvements in both the image quality and the diagnostic performance of CCTA. The international joint guidelines recommend the specifications of MDCT systems for cardiac CT to perform appropriate CT examinations.\(^4\)

**12.1.1 Wide-Coverage MDCT**

Wide-coverage MDCT in the z-axis direction has the further advantage of reducing the image acquisition time. In fact, while a 64-row CT scanner (i.e., the minimum requirement for CCTA) can obtain coronary artery images in 5–8 s, the entire image of the heart is obtained in ≤1 s using the 256-row or 320-row CT scanners, because their detector width of 16 cm covers the whole heart with a single rotation of the tube. Shortening of the image acquisition time helps reduce the breath-holding time and heart rate variation during image acquisition. Therefore, it reduces banding artifacts and misalignment of the CT dataset, maintaining coronary artery continuity, which in turn contributes to good image quality.

**12.1.2 Temporal Resolution**

Temporal resolution generally refers to the “discrete resolution of a measurement with respect to time” and is defined as the amount of time needed to revisit and acquire data for the exact same location on the CT image. Cardiac CT can obtain clear images of the heart and coronary arteries with a high temporal resolution. When ECG-gated scanning is performed, a 360-degree CT image can be reconstructed from the projection data with approximately half a rotation (actually 180 degrees + fan angle) of the X-ray tube using the half-reconstruction algorithm. Therefore, the temporal resolution is approximately half the speed of the X-ray tube rotation speed. The abovementioned guidelines also recommend the use of a MDCT system with a tube rotation speed ≤0.35 s for cardiac CT. Current available cutting-edge MDCT scanners are equipped with an even faster gantry rotation speed (0.25–0.28 s) and achieve better temporal resolution. In addition, a dual-source CT system has 2 X-ray tubes and 2 corresponding detectors (mounted onto the rotating gantry with an angular offset of 90 degrees), and can obtain the half-reconstruction images with double the temporal resolution.
When a single phase is reconstructed from a combination of several cardiac cycles using the multisector reconstruction algorithm, the time required for each imaging sector is reduced, and the temporal resolution is increased.

### 12.1.3 Spatial Resolution
Spatial resolution refers to the distance between or the ability with which 2 different objects, which are either close altogether or small in pixel size in a digital image, can be distinguished. Considering a 64-row CT can obtain CT images with a slice thickness of 0.5–0.625 mm, whereas some MDCT scanners can do so with a spatial resolution of 0.35 mm in the XY direction, the distortion-free CT volume data with isotropic voxels can be utilized in clinical practice. In addition to slice thickness, multiple other factors also influence the spatial resolution, including image parameters such as the tube voltage and tube current, gantry rotation speed, and the number of sampling views. Thus, CT vendors have aimed at improving the spatial resolution by taking into consideration the various features of each MDCT scanner. To date, spatial resolution has been improved by increasing in the number of sampling views through a fine tube focal spot deflection (double sampling) for the X-axis or Z-axis direction and/or high-speed data sampling.

Furthermore, an ultra-high resolution CT scanner launched in 2017 is capable of resolving the anatomy to 0.15 mm in the XY direction, resulting in fine volume data with a slice thickness of 0.25 mm. This shows promise for improving the diagnostic accuracy of small vessel disease, with a slice thickness of 0.15 mm in the XY direction, resulting in fine volume data with a slice thickness of 0.25 mm. This shows promise for improving the diagnostic accuracy of small vessel disease, in-stent restenosis, and calcified lesions. Nevertheless, CCTA remains inferior to invasive coronary angiography in terms of both temporal and spatial resolution. In addition, several problems, including motion artifacts resulting from insufficient temporal resolution, misregistration artifacts because of improper segmental reconstruction, and beam hardening artifacts derived from high attenuation structures (e.g., stents and calcification), are yet to be overcome. Therefore, CCTA cannot completely replace invasive coronary angiography at present.

### 12.1.4 Iterative Reconstruction
Up until recently, CT images have been mostly reconstructed with FBP, which can reconstruct CT images rapidly using a simplified model, but shows increased image noise. Iterative reconstruction is a method of image reconstruction in which a first estimate image is created and then errors between the calculated raw data by a forward projection step considering the system geometry and the measured raw data, followed by repeated updating of the reconstructed image so that errors are minimized. This technique decreases the image noise and can be used to improve the quality of images obtained with a normal radiation dose, as well as to maintain image quality with a lower dose CT scanning.

### 12.2 Image Acquisition and Image Reconstruction
#### 12.2.1 ECG-Gated Image Acquisition
The following 2 methods have been implemented for ECG-gated image acquisition: (1) retrospective and (2) prospective. In the former, the scanning is performed while simultaneously recording an ECG, and the CT images reconstructed from the target cardiac phase are obtained after scanning. In the latter, image acquisition (X-ray exposure) is performed only for a specific cardiac phase, which is set by the predetermined time from the R wave. Although retrospective ECG gating was the standard method in the early days of CCTA, its related increase in radiation exposure (the X-ray is exposed during the unneeded phases for evaluation) is concerning. To reduce the radiation dose, the X-ray exposure should be optimized to the required cardiac phase to obtain a still image according to the scan heart rate (dose modulation).

Prospective ECG-gated scanning minimizes radiation exposure because scanning (X-ray exposure) is only performed during a specified cardiac phase. Therefore, it has become the standard method of CCTA for the appropriate scan heart rate. Given that both the target heart rate and the cardiac phase depend on the temporal resolution of the MDCT scanner and image reconstruction method, knowledge of ECG-gated cardiac CT is essential. With regard to cardiac physiology, as the coronary and myocardial blood flow predominantly increase during diastole, image acquisition at mid-diastole is desirable (low heart rate), whereas the end-systolic phase is generally included in the acquired cardiac phase when the patient's scan heart rate is higher.

### 12.2.2 Noncontrast Cardiac CT
Noncontrast cardiac CT refers to ECG-gated noncontrast CT scanning and mainly evaluates the extent of coronary artery calcification. Conventionally, electron-beam CT was used to evaluate coronary artery calcification, but recently MDCT can achieve similar accuracy after appropriate adjustment of the scanning conditions. Indeed, most MDCT scanners used for CCTA can satisfy these requirements. Specifically, prospective ECG-gated scanning, with a slice thickness of 2.5–3 mm, using a MDCT scanner with 4 or more detector rows and a gantry rotation speed of at least 0.5 s, are endorsed for the assessment of coronary artery calcification. Moreover, the target cardiac phase should be set at the early to mid-diastolic phase and scanning should be performed while the patient is breathing.

### 12.2.3 Contrast Injection Protocol
Adequate contrast enhancement of coronary arteries is essential for reliable evaluation using CCTA. Considering that optimal images require a high intra-arterial attenuation (>250 Hounsfield units [HU]), contrast medium with high iodine concentrations (270–400 mg iodine/mL) and intravenous administration (injection rate: 4–7 mL/s) are preferred in adults. A slower infusion rate may be acceptable in some patients with small body size, who can undergo low-voltage scanning. Generally, the duration of the contrast injection should be longer than the scanning time (≥10s) and a 20G cannula should be used.

Intracoronary attenuation significantly modifies the attenuation of coronary atherosclerotic plaques assessed with CCTA. Therefore, the protocol for contrast injection should be modified to achieve appropriate CT values. Because the patient’s body size (body weight and body surface area) and cardiac function also influence contrast enhancement, collecting relevant information from the patient prior to the cardiac CT examination is recommended.

### 12.2.4 Premedication
Appropriate premedication of the patient is helpful to
obtain high-quality CT images with most of the current MDCT scanners. This section outlines the use of β-blockers and nitrates for heart rate control and clear coronary artery delineation, respectively. The use of β-blockers for heart rate control has 2 advantages: (1) lowering the scan heart rate, which allows for still images and (2) allows the use of prospective ECG-gated scanning to minimize radiation exposure.

Beta-blockers are selected by considering the drug’s half-life as well as β₁-selectivity (to reduce the risk of provoking asthma). They are generally administered either orally or intravenously. For example, metoprolol (a β₁-selective agent) is administered orally at 1 hour before CT examination, at a dose of 20–100 mg, depending on the patient’s body weight and baseline heart rate. In the case of insufficient effect, additional metoprolol may be given either orally or intravenously at the time of examination. In contrast, landiolol hydrochloride is a β₁-selective intravenous drug with a short half-life (~4 min; its use for CCTA is covered by insurance in Japan). It can be administered immediately before scanning in the CT room, given its short-acting effect.

Nitrates act directly on the vascular smooth muscle to dilate coronary arteries, thus contributing to an improvement in coronary artery stenosis diagnosis. Either sublingual nitroglycerin tablets (0.3 mg/tablet) or sublingual sprays (0.3 mg/dose) are used. Considering that the heart rate transiently increases immediately after administration, nitrates are preferably given 5 min prior to CCTA. When used at the same dose, sublingual sprays exert a stronger vasodilatory effect than sublingual tablets. Furthermore, sublingual tablets should be used with caution because their absorption can be variable. Accordingly, the administration of 2 puffs of sublingual spray (0.6 mg: equivalent to 1 mg of isosorbide dinitrate by intracoronary administration) is recommended. Contraindications to nitrates include severe hypotension, severe aortic stenosis, and angle closure glaucoma, as well as patients taking phosphodiesterase inhibitors.

12.2.6 Image Reconstruction
Spatial resolution of CT images is influenced by both the specifications of MDCT (e.g., slice thickness and number of sampling views) and the image reconstruction. In the process of image reconstruction that generates tomographic images from X-ray projection data, CT images are generated through the aforementioned FBP or iterative reconstruction method. In addition, this is combined with dedicated filtering processes (i.e., reconstruction kernel, also referred to as the “filter”). Although CT images for CCTA are generally reconstructed with a smooth vascular kernel, a sharper kernel that handles high-frequency data is applied when assessing calcified lesions or coronary stenoses. Although the images reconstructed with a sharp kernel have better spatial resolution, increased noise is produced. Therefore, a sharp kernel is not suitable for the evaluation of structures with low CT values such as noncalcified plaques.

12.3 Radiation Exposure
A European epidemiology group reported that Japan had the highest risk of cancer attributable to diagnostic X-ray (i.e., 3.2% among 15 developed countries). Similarly, another report discussed the risk of developing cancer as a result of CCTA using 64-row scanners. Given that most cardiac CT requires thin slices and a highly overlapping scan, the radiation exposure to the field of view is relatively high. Here we outline the basic characteristics and management of radiation exposure, as well as its reduction.

12.3.1 Radiation Protection and Management
Radiation protection is based on the application of 3 principles: justification, optimization, and limitation. Justification suggests that “no practice involving exposure to radiation should be adopted unless it produces sufficient benefit to the exposed individual or to society to offset the detriment it causes”. In contrast, optimization implies that “exposure to radiation should be as low as reasonably achievable”. With regard to the medical exposure of patients to radiation, applying dose limits or constraints is not appropriate, given that limits would often do more harm than good. However, considering the potential benefits of CT examinations, making an effort to optimize and reduce the radiation dose is essential.

12.3.2 Exposure Dose Unit and Evaluation Methods
Radiation exposure can be assessed through both the absorbed dose and the effective dose. Although the absorbed dose (expressed in Gy) can be measured using a dosimeter, managing it in clinical practice is difficult. Furthermore, several indices can be used to estimate the absorbed dose, including the CTDIvol and the DLP. The CTDIvol is a numerical value (expressed in mGy) that is calculated by integrating over the dose profile for a single axial rotation, then dividing by the nominal beam width. In contrast, the DLP is the product of the CTDIvol and the scan length of a group of scans (expressed in mGy·cm). These parameters are generally listed in the dose reports for MDCT scanners. The effective dose (expressed in Sv) is the product of the DLP and a weighting factor for the target region of the scanning. This index is adopted when comparing the risk of radiation exposure between CT and other imaging modalities.
12.3.3 Risks of Radiation Exposure Associated With CT

Radiation exposure is known to produce a wide variety of biological damage. Although radiation doses >100 mGy clearly increase the incidence of cancer in humans, evidence that lower doses increase the risk of cancer is lacking. Nonetheless, not to underestimate the risk of radiation exposure, the potential risk of carcinogenesis should be considered even at the lowest dose (the linear no-threshold hypothesis). However, with exposure to doses exceeding 100 mSv, the approximate overall fatal risk coefficient of developing cancer is estimated to increase at a rate of 0.5% per 100 mSv. In contrast, a recent epidemiological study estimated that the lowest carcinogenic dose was 10–50 mSv for acute exposure and 50–100 mSv for chronic exposure.495

12.3.4 Factors Influencing the Radiation Dose

a. Scan Parameters

These parameters include the X-ray tube voltage, tube current, gantry rotation speed, and pitch. With the standard tube voltage of 120kV, the guidelines of the Society of Cardiovascular Computed Tomography (SCCT) recommend low-voltage scanning combined with an iterative reconstruction technique, as mentioned earlier. For example, a tube voltage of 100 kV is recommended for patients with either a body weight ≤100 kg or a BMI ≤30 kg/m², whereas a voltage of either 100 kV or 80 kV is recommended for children and adults with a small body size.486 Note that the tube current should be adjusted according to both the patient’s size and the target organ. The radiation exposure increases if a greater overlapping scan is performed using a smaller helical pitch.

b. Image Quality and Radiation Exposure

Generally, image quality is closely proportional to the radiation dose; that is, as the radiation dose decreases, the image quality decreases. When other factors interfere with image quality, increasing the radiation dose is necessary. Therefore, it is important to minimize the radiation dose while avoiding a remarkable decrease in image quality. In young patients (children) and women, who are particularly susceptible to radiation and may have a higher lifetime risk of cancer, the indications for CT examinations should be carefully considered.496

According to previous reports, radiation exposure in CCTA is approximately 8–15 mSv, which is higher than that observed with invasive coronary angiography (3–6 mSv). Other previous studies suggested that CCTA combined with dose automatic modulation, as well as a noise reduction filter, resulted in decreased radiation exposure (=3–8 mSv). Depending on the patient’s size and scan heart rate, the abovementioned techniques to minimize radiation exposure can be combined with the latest CT technologies (e.g., area-detector CT or dual-source CT) and reduce the radiation dose for CCTA to around 1–3 mSv.

12.4 Adverse Reactions to Contrast Medium

12.4.1 Allergic Reactions

Adverse reactions to iohinated contrast medium occur in approximately 3% and 0.04% of patients, who develop mild and severe symptoms, respectively. Furthermore, lifethreatening adverse reactions affect 1 in 170,000 patients.497 Initial screening for risk factors associated with serious adverse reactions is essential and includes the patient’s history of allergy (atopy and food allergy, etc.), which is associated with an approximately 2-fold increase in the incidence of reactions; history of bronchial asthma (=10-fold increase); previous moderate or severe reaction to a contrast agent (=4 to 5-fold increase); and serious heart disease (=3-fold increase).498 Although compliance with institutional guidelines is required, contrast medium should be administered carefully in patients with a history of noncontrast allergic reactions. It is contraindicated for patients with asthma, prior moderate/severe contrast agent reaction, or serious heart disease. Serious contrast allergic reactions can occur even in patients who did not present any adverse reaction during previous contrast CT examinations. Therefore, the CT room has to be staffed with appropriately trained personnel and should include an emergency cart equipped with commonly used drugs (adrenaline and H1 blocker anti-histamines) to promptly handle contrast allergic reactions.

12.4.2 Contrast-Induced Nephropathy and CKD

According to the 2012 joint committee guidelines, contrast-induced nephropathy (CIN) is defined as an “increase in serum creatinine (Cr) by ≥25% from baseline or by ≥0.5 mg/dL within 72 hours after contrast administration”499 Use of the eGFR is recommended for the assessment of renal function (eGFR = 194 x Cr−1.094 x age−0.287 [×0.739 for women]). Specifically, eGFR and urinary protein are used to classify CKD. Generally, patients with impaired renal function are more likely to develop acute renal failure due to CIN after contrast administration. Therefore, the guidelines also recommend contrast-enhanced CT to be performed carefully with precautions for patients with an eGFR <45 mL/min/1.73 m². Examples include reducing the amount of contrast medium or giving a preventive saline infusion. With regard to high-risk patients, an intravenous saline infusion at 1 mL/kg/h is generally recommended 6 hours prior to and 6–12 hours following the administration of the contrast agent.499

For diabetic patients, discontinuing biguanides 48 hours prior and 48 hours following the administration of the contrast medium is suggested, because biguanides may provoke lactic acidosis due to drug interaction.499 In addition, an increase in the risk of CIN may be observed in patients with dehydration, diabetes mellitus, congestive heart failure, or renal dysfunction, as well as in elderly patients. Previous studies also report that CIN is associated with increased mortality, including death from recurrence of CAD.500

Although β-blockers are widely used in CCTA, a previous study suggested an increase in the incidence and seriousness of adverse reactions to contrast medium in patients receiving premedication with β-blockers.501 However, given that the study population involved patients with cardiac disease, further investigations are required to clarify whether β-blockers increase the risk of reactions to contrast medium in patients undergoing routine CCTA. Incidentally, anaphylactic reactions to the contrast medium are sometimes refractory to the usual dose of epinephrine in patients taking β-blockers. Therefore, it is important to know that glucagon may benefit patients with severe adverse reactions to contrast medium.502

12.5 Indications (Table 33)

Several professional societies and joint committees have proposed appropriate use criteria regarding CCTA in a
variety of clinical scenarios: (1) general use of cardiovascular CT, \(^{484}\) (2) CCTA in patients with chronic chest pain (including other diagnostic tests), \(^{503,504}\) and (3) multimodal diagnostic tests for stable coronary heart disease. \(^{505}\) The SCCT has suggested CCTA guidelines on radiation dose and dose-optimization strategies, \(^{506}\) the scanning protocol, \(^{486}\) as well as the interpretation and reporting. \(^{485}\)

The Japanese Circulation Society and the multi-societies joint working groups published both the Guidelines for Noninvasive Diagnosis of Coronary Artery Lesions (JCS 2009) and the Guidelines for Diagnostic Evaluation of Patients with Chronic Ischemic Heart Disease (JCS 2010). \(^{49}\) These describe the basics behind CCTA and its clinical applications.

Given that CCTA involves a risk of radiation exposure and adverse reactions to the contrast medium, the indications must be individually and carefully considered. The most appropriate candidates for such an assessment are asymptomatic patients with suspected stable coronary artery disease, who have an intermediate pretest probability and present uninterpretable ECG or any difficulties with exercise stress testing. On the other hand, it is not appropriate to perform CCTA in asymptomatic patients, who have a low pretest probability, or present interpretable ischemic ECG changes in addition to de novo patients. CCTA may also be useful in patients who have undergone prior revascularization therapy (e.g., CAGB or coronary stenting with stent diameter \(\geq 3\) mm \(^{507}\) \(^{508}\) ), and to those with known or suspected congenital coronary artery anomalies. \(^{509}\)

Estimating the pretest probability plays an important role in the diagnostic testing for coronary artery disease. The following 2 methods are mainly used to determine such a probability. One method is based on large-scale epidemiological studies conducted in the USA using several factors, including age, sex, symptoms, and coronary risk factors (Duke score or Framingham risk score). The other method is based on a Japanese epidemiological study (NIPPON DATA) that can calculate the 10-year risk of death from stroke and coronary artery disease, including myocardial infarction and angina pectoris. \(^{510}\) \(^{512}\)

### 12.6 Noncontrast Cardiac CT

#### 12.6.1 Coronary Artery Calcification

Coronary artery calcification is a pathogenic process occurring during stabilization of atherosclerotic plaques, forming as a result of chronic vascular inflammation and metabolic factors. The extent of coronary artery calcification correlates with the severity of coronary atherosclerosis, and can be used to predict future cardiovascular events. \(^{513}\)

<table>
<thead>
<tr>
<th>Table 33. Recommendations and Levels of Evidence for CCTA</th>
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<tbody>
<tr>
<td><strong>1. Asymptomatic</strong></td>
</tr>
<tr>
<td><strong>CACS (risk stratification)</strong></td>
</tr>
<tr>
<td>Low pretest probability of CAD</td>
</tr>
<tr>
<td>Intermediate pretest probability of CAD</td>
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<tr>
<td>High pretest probability of CAD</td>
</tr>
<tr>
<td><strong>CCTA (detection of coronary artery stenosis)</strong></td>
</tr>
<tr>
<td>Low pretest probability of CAD</td>
</tr>
<tr>
<td>Intermediate pretest probability of CAD</td>
</tr>
<tr>
<td>High pretest probability of CAD</td>
</tr>
<tr>
<td><strong>2. Symptomatic or clinical scenario equivalent to myocardial ischemia</strong></td>
</tr>
<tr>
<td><strong>CCTA (detection of coronary artery stenosis)</strong></td>
</tr>
<tr>
<td>Low pretest probability of CAD, ECG uninterpretable or unable to exercise</td>
</tr>
<tr>
<td>Intermediate pretest probability of CAD, ECG uninterpretable or unable to exercise</td>
</tr>
<tr>
<td>High pretest probability of CAD, ECG uninterpretable or unable to exercise</td>
</tr>
<tr>
<td>Suspected vasospastic angina</td>
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<tr>
<td><strong>Unstable angina/non-ST-elevation acute myocardial infarction</strong></td>
</tr>
<tr>
<td>Low-to-intermediate likelihood (no ECG ischemic change, biomarker test negative)</td>
</tr>
<tr>
<td>High likelihood (ECG ischemic change, biomarker test positive)</td>
</tr>
</tbody>
</table>

(Table 33 continued the next page.)
For example, Agatston et al identified significant calcified lesions determined by a CT value ≥130 HU and a size ≥2 pixels. They defined the summed area score of each calcified area multiplied by an attenuation factor, according to the maximal CT value of the lesion, as CACS or AS. Specifically, the CACS can be quantified by the following 3 methods: AS, volume score, and mass score. Although age, sex, and ethnicity influence the prevalence and extent of CACS, some studies have reported CACS as both an independent predictor of future cardiovascular events and a useful diagnostic tool combined with the pretest probability for reclassification of patients suspected of CAD.

Recent studies have demonstrated that pericardial fat is a significant risk factor for future coronary events independent of traditional coronary risk factors and the CACS, providing complementary information from noncontrast cardiac CT.

12.6.3 Fatty Degeneration in the Myocardium
Fatty degeneration (also called fat deposition) in the myocardium can be observed in patients with OMI and cardiomyopathy. Fatty degeneration develops over time during the occurrence of myocardial necrosis, damage, or fibrosis. When it is observed predominantly in the subendocardial layer corresponding to the territory of a coronary artery, it is suggestive of OMI.

12.6.2 Visceral Fat and Pericardial Fat
Adiponectin is a hormone that promotes insulin sensitivity and has an anti-inflammatory effect. Abundant visceral and pericardial fat results in reduced adiponectin secretion and induces atherosclerosis (caused by various inflammatory cytokines secreted from adipose tissue). Recent studies have demonstrated that pericardial fat is a significant risk factor for future coronary events independent of traditional coronary risk factors and the CACS, providing complementary information from noncontrast cardiac CT.
12.7 Interpretation and Reporting of CCTA

12.7.1 Analysis
CCTA should be analyzed and reviewed using dedicated workstation software for 3-dimensional assessment of the heart. Given the complexity of coronary artery anatomy, observing multiple cross-sectional images and various image formats is important. The interpreters should be familiar with the basics of CT image reconstruction, the use of workstations, and the advantages and limitations of the displayed image formats. The SCCT guideline recommends appropriate image reformat for the assessment of CCTA (Figure 8), as follows: “Recommended” (axial tomogram, multiplanar reformations [MPR], and maximum intensity projections [MIP]); “Optional” (curved planar reformations [CPR]), and “Not recommended” (volume

Figure 9. Coronary artery segment model according to the AHA classification. Main coronary vessels: LM, left main coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary. Major branches: D1, first diagonal branch; D2, second diagonal branch; OM, obtuse marginal branch; PL, posterolateral branch; PD, posterior descending branch; RPD, right posterior descending branch. Minor branches: AC, atrial circumflex branch; AM, acute marginal branch; AV, atrioventricular node branch; CB, conus branch; RV, right ventricular branch; SN, sinus node branch. The intermediate branch artery is generally assigned to segment number 16. (Reproduced from Austen et al 1975, 524 with permission. Copyright (1975) by American Heart Association.)

Figure 10. Coronary segmentation diagram of the Society of Cardiovascular Computed Tomography (SCCT). Main coronary vessels: LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery; RCA, right coronary. Major branches: D1, first diagonal branch; D2, second diagonal branch; OM1, first obtuse marginal branch; OM2, second obtuse marginal branch; L-PLB, posterolateral branch from LCX; R-PLB, posterolateral branch from RCA; L-PDA, posterior descending branch from LCX; R-PDA, posterior descending branch from RCA; RI, ramus intermedius. (Reproduced from Leipsic et al 2014, 485 with permission from Elsevier. Copyright (2014) by Society of Cardiovascular Computed Tomography.)
rendering [VR]). An angiographic view that allows the cardiac chambers to be viewed without contrast medium is useful for the MIP image format. Although the VR image reformat is not suitable for quantification of coronary stenosis severity, it allows an east review of the entire heart, including coronary anatomy and stenotic lesions.

12.7.2 Coronary Anatomy
CCTA provides 3D images that facilitate the understanding of the anatomical relation between coronary arteries and the surrounding structures, as well as of the origin and course of coronary arteries, their branches, and coronary dominance. The use of CCTA will be most beneficial to patients with coronary anomalies.

Coronary artery segmentation is necessary for accurate description in the report and is commonly based on either the AHA model or the SCCT model (Figures 9, 10). The SCCT model has adopted some modifications of the AHA model, including the variations in the anatomy of the distal right and circumflex coronary arteries. Both models are easy to use because of their systematic nature. It is desirable to standardize the segmentation classification and reporting used at each center (i.e., between the attending physicians and diagnosticians).

12.7.3 Coronary Artery Stenosis
When coronary artery stenosis is evaluated with CCTA, the stenosis severity is assessed by measuring the luminal diameter of the stenotic region and of the nearby healthy proximal and distal sites on the cross-sectional images. For accurate evaluation, observing multiple display images in a complementary manner is useful (Figure 11). A meta-analysis demonstrated that the diagnostic ability of 64-row CT or dual-source CT for coronary artery stenosis (>50%) was sufficient for excluding significant stenosis with a sensitivity of 89%, specificity of 96%, positive and negative predictive values of 78% and 98% (Table 34). Although the quantitative assessment of CCTA is generally well correlated with that of invasive coronary angiography and IVUS, relatively large standard deviations are seen (±25% at best).

Accordingly, the SCCT guidelines recommend a stepwise evaluation of the stenosis (Table 35). With regard to the morphological assessment of coronary artery stenosis (≥50%) using CCTA, a 5-year follow-up international registry of 1,884 patients from 12 centers showed an association between an increase in the number of significant CAD and a higher incidence of future cardiac events. Similarly, it has been suggested that the event rate in patients with significant (36.3%) or nonsignificant (13.2%) stenosis was significantly higher than that in patients without coronary lesions (5.6%).

The assessment of coronary artery stenosis and myocardial ischemia is essential for both identification of the culprit lesion and decision-making for coronary revascularization. A single-center study reported that the sensitivity and specificity of CCTA (≥50% stenosis) to detect hemodynamically significant CAD (invasive FFR <0.8) were 45% and 79%, respectively. In contrast, when myocardial ischemia assessed by stress myocardial perfusion imaging by SPECT (PET) was defined as the reference standard, previous data from multiple centers described the positive and negative predictive values of CCTA (≥50% stenosis) as 29–44% and 88–100%, respectively. Therefore, single...
evaluation by CTA is often insufficient to determine the indications for revascularization therapy, although CCTA is useful for excluding significant CAD lesions with myocardial ischemia. In the case of ≥50% CTA-stenosis or myocardial ischemia, it is useful for excluding significant CAD lesions with indications for revascularization therapy, although CCTA evaluation by CTA is often insufficient to determine the importance of CTA-based plaque assessment.443

**12.7.4 Coronary Plaque**

CCTA can evaluate extraluminal plaques associated with vascular remodeling and can be used to differentiate plaque subtypes (e.g., calcified, noncalcified, and partially calcified plaque). The SCCT medical terminology guidelines recommend using “noncalcified” plaque composition, rather than “soft” or “lipid-rich”, because the low intravascular plaque CT values do not always correlate with the pathological findings.540 Recent CCTA studies described vulnerable plaque (“high-risk plaque”) characteristics that are independently associated with future ACS. They include (1) low-attenuation plaque <30 HU, (2) positive remodeling >1.1, (3) “napkin-ring” sign, and (4) spotty calcium deposits. When ≥2 of these findings are present, it should be reported as high-risk plaque.540 When a β-blocker is administered to reduce the scan heart rate, it should be done with caution because reduced myocardial contractility results in increased LVESV and reduced LVEF and cardiac output.545

**12.7.6 Noncoronary and Extracardiac Findings**

In addition to the coronary anatomy, cardiac CT enables simultaneous assessment of the surrounding noncoronary and extracardiac structures (e.g., cardiac valves, myocardium, aorta, and superior/inferior vena cava, and the field of view includes parts of the lungs, mediastinum, and digestive organs). Reviewing all the visible findings is essential because (1) primary or secondary lesions from noncoronary disease may be detected and (2) noncardiovascular disease may become the final diagnosis.445 Triple-rule-out CTA for acute chest pain can be an effective evaluation of acute myocardial infarction, aortic dissection and pulmonary thromboembolism. Two-phase CT is a reliable method for detecting intracardiac thrombi, including the left atrial appendage, in patients with a history of cardiac dysfunction or arrhythmia.

In addition, the systematic evaluation and diagnostic algorithm of extracardiac findings from further evaluation to follow-up should be considered, as some patients with high pretest probability of CAD may overlap with those presenting extracardiac findings including malignant neoplasm.544,547 From the viewpoint of radiation exposure...
reduction, narrowing the field of view and maximizing the range of reconstruction images are desirable to allow the evaluation of optimized images.

12.7.7 Coronary Artery Disease Reporting and Data System (CAD-RADS)
Since 2016, a reporting system for CAD using cardiac CT has been proposed by 3 academic societies, based on the SCCT guidelines. The CAD-RADS classifies the stenosis severity of CAD lesions using a 6-point scale (from 0, no stenosis to 5, occluded) as the interpretation in the report and provides patient-specific recommendations with common terms and reporting phrases. The recommendations for further testing for stable and acute chest pain are based on the outcomes of several recent large-scale multicenter studies. The CAD-RADS is promising with regard to improving consistency in patient care by both facilitating communication among healthcare professionals and accumulating the data for education and clinical research.

12.8 Functional Evaluation and New Technologies
In addition to morphological assessment of coronary artery stenosis and plaque, some researchers and clinical studies have been investigating functional assessment using cardiac CT and some diagnostic tools have already been established. This section will introduce the functional assessments and new technologies beyond conventional assessment using CCTA.

12.8.1 Image Fusion
Cardiac image fusion (hybrid imaging) can be obtained using a combination of anatomical (coronary anatomy and stenosis) and functional (e.g., myocardial perfusion imaging or metabolic imaging) information by 3-dimensionally superimposing CCTA and SPECT (or PET). Some studies have demonstrated that image fusion is beneficial for decision-making and prognostic evaluation. However, it is controversial whether this method is clinically beneficial in terms of added value, relative to the increased radiation exposure and costs using CT and radionuclide examinations. Nevertheless, image fusion may be helpful for further investigating the anatomical relationship between CTA-based coronary artery stenosis and SPECT-derived dysfunction territory such as in myocardial ischemia.

12.8.2 CT Perfusion
Cardiac CT can also evaluate myocardial ischemia by assessing the contrast enhancement of the myocardium (CT perfusion: CTP) during pharmacological stress (e.g., ATP, adenosine, etc.). The methods used are generally dependent on the detector-range of MDCT and the number of data acquisitions. Static CTP imaging can evaluate myocardial ischemia with a hypo-enhanced (hypoperfusion) area in a snapshot (single-volume dataset) during the first-pass perfusion of contrast medium. In contrast, dynamic CTP can evaluate myocardial ischemia with quantitative parameters, including myocardial blood flow. This is possible by analyzing the time-attenuation curve of the myocardium using wide-detector MDCT, ideally covering the entire left ventricle. Many single-center and multicenter studies have shown that (1) stress CTP can detect significant CAD lesions and myocardial ischemia with noninferior ability to SPECT and MR, (2) stress CTP can add value to CCTA, and (3) the diagnostic ability for myocardial ischemia is equivalent between adequately performed static CTP and dynamic CTP. Cardiac CT can also describe myocardial infarction as either a perfusion defect in the early phase or as late iodine enhancement (LIE) in the late phase (e.g., after 5–8 min), allowing for assessment of myocardial viability.

The SCCT guidelines refer to the clinical effectiveness of stress CTP for detecting significant CAD lesions with high diagnostic performance. Stress CTP is a promising tool for further evaluation of patients with moderate or more coronary stenosis or nondiagnostic lesions using a single modality. In addition, it presents an alternative to stress myocardial perfusion imaging (e.g., SPECT). However, stress CTP is not always necessary for all patients who undergo CCTA. If CCTA and stress CTP are performed in a single session, low-dose scanning should be applied in a comprehensive protocol, taking into consideration the issues associated with increased radiation exposure and contrast dose.

12.8.3 Dual-Energy CT
Dual-energy CT creates 2 views (2 different CT attenuation images) per location at 2 different energies (e.g., 2 different tube voltages) and can characterize the chemical composition of a material. Dual-energy CT scanning can be performed with several technologies, including dual-source CT: high-speed tube voltage switching (rapid kV switching), and dual-layer CT. Some studies have suggested that dual-energy CT can evaluate both myocardial ischemia by calculating the contrast concentration in the myocardium (i.e., myocardial blood flow) and myocardial infarction by increasing the LIE in the late images.

12.8.4 FFR-CT
FFR-CT is a novel simulation algorithm to calculate coronary flow and pressure fields in a hyperemic state from static CT images using computational fluid dynamics, image-based modeling, and cardiac physiology. The algorithm estimates the resting coronary blood flow and microvascular resistance using accurate anatomy of the coronary arteries and left ventricle. Furthermore, it assumes a hyperemic state during virtual pharmacological stress loading and hemodynamic change, to calculate the pressure difference across a coronary artery stenosis, which corresponds to invasive FFR as a ground truth (see section “13. Fractional Flow Reserve (FFR)-CT” for details).

12.8.5 New Technologies
Some research groups have investigated the feasibility of new technologies such as subtraction CCTA for calcified lesions, transluminal attenuation gradient (TAG) of CCTA, and automatic quantification of CTA-based coronary artery territory mapping. Although all the technologies are promising, further investigation is needed to ensure their clinical applications.

13. Fractional Flow Reserve (FFR)-CT

13.1 Background
Measurement of FFR enables prediction of the effect of coronary revascularization. The cutoff value for FFR was initially reported to be 0.75, which showed the best correlation with stress tests such as stress myocardial imaging.
The FAME trial (n=1,005) showed that FFR-guided (cutoff value: 0.8) PCI was associated with a significantly lower incidence of major cardiovascular events than standard PCI based on the extent of stenosis revealed by invasive coronary angiography (13.2% in the FFR-guided PCI group vs. 18.3% in the standard PCI group, P=0.02), and that the cost of care during the 1-year follow-up was significantly lower with FFR-guided PCI than standard PCI (14,315 USD vs. 16,700 USD, P<0.001).

In addition, the FAME 2 study (n=1,220) revealed that treatment of myocardial ischemia detected by FFR with PCI and optimal drug therapy was associated with less emergency revascularization than optimal drug therapy alone (1.6% vs. 11.1%, P<0.001). However, measuring FFR with a pressure wire during cardiac catheterization requires intravenous or intracoronary drug administration to induce maximal hyperemia, adds to the time and cost of investigation, and is an invasive procedure associated with catheter manipulation. Against this background, FFR-CT has recently been developed as a method for noninvasively calculating the FFR by applying fluid dynamics to data from CCTA (Figure 12), and it is becoming an option for assessment of myocardial ischemia in Western countries.

### 13.2 Basic Concept

FFR-CT uses a mathematical model based on fluid dynamics that integrates patient-specific imaging data with a population physiology model to solve the equations governing blood flow and calculate the blood flow velocity and pressure in the target vessel during simulated hyperemia. Software programs have been developed that can solve the Navier-Stokes equation and simulate patient-specific arterial models, and these have been applied to FFR-CT of the coronary arteries. For example, the HeartFlow FFR-CT method involves acquisition of CCTA data, assessment of image quality, and use of an image segmentation algorithm to extract 3-dimensional models of the proximal aorta and coronary arteries. Next, the left ventricular myocardial volume is calculated to assess overall coronary blood flow demand, after which physiological models of aortic pressure and microcirculatory resistance are created in the order of the resting state followed by maximal hyperemia. Finally, the blood flow and pressure under simulated maximal hyperemia are calculated.

![Figure 12. A 65-year-old Japanese male with abnormal ECG underwent CCTA, FFR-CT and invasive FFR (patient in the NXT trial). CCTA presented >50% stenosis of the right coronary artery (RCA) and the left circumflex (LCx) artery second obtuse marginal branch (OM2). However, FFR-CT showed no ischemia, with RCA FFR-CT=0.88 and LCx OM2 FFR-CT=0.95. Invasive FFR confirmed that the lesions were nonischemic, with FFR=0.93 in the RCA and FFR=0.99 in the LCx OM2. (Reproduced from Miyoshi et al 2015, with permission.)](image-url)
calculated for a patient-specific model, and the FFR-CT value (the ratio of mean coronary pressure to mean aortic pressure) is calculated from the pressure field using fluid dynamics.\(^5\)\(^6\)

### 13.3 Importance of CCTA Imaging Protocol and Image Quality

Because FFR-CT analysis is used to predict the standard invasive FFR, it is necessary to administer nitrates to minimize the difference in vessel diameter between CCTA and cardiac catheterization. It is also important to optimize the imaging protocol to achieve adequate spatiotemporal resolution, and to calculate the luminal diameter by fine image segmentation despite the presence of calcification, motion, and other artifacts.

FFR-CT analysis uses standard CCTA data, so it is crucial to adhere to the SCCT guidelines on CCTA imaging\(^4\)\(^6\) in order to obtain high-quality images that are suitable for 3D reconstruction and quantitative analysis. It is ideal to use a \(\beta\)-blocker to reduce the heart rate and perform imaging at a heart rate of \(<60\) beats/min. It is also desirable to perform reconstruction of images by limiting the field of view to the heart, using a spatial resolution of \(\geq 0.4–0.5\) mm, and having a slice thickness of \(<1\) mm.\(^2\)\(^8\)

The spatial resolution of standard CCTA is generally sufficient to provide an anatomical model for FFR-CT analysis. However, poor image quality may interfere with interpretation of CCTA data and compromise the segmentation required for FFR-CT modeling (misalignment artifacts). A secondary analysis of the DeFACTO study (described later) demonstrated that administration of \(\beta\)-blockers and sublingual nitroglycerin within 30 min before imaging improved the specificity of FFR-CT (66.0% with a \(\beta\)-blocker vs. 51.0% without a \(\beta\)-blocker; \(P=0.03\); 75.0% with nitroglycerin vs. 54.0% without nitroglycerin, \(P=0.013\)). The presence of misalignment artifacts decreased sensitivity from 86.0% to 43.0% (\(P=0.001\)), but the presence/absence of motion artifacts and the extent of coronary artery calcification did not influence diagnostic performance.\(^5\)\(^7\)

### 13.4 Reproducibility

A secondary analysis of the NXT study (described later) examined the reproducibility of FFR-CT and standard FFR analysis in 28 patients (58 lesions) who twice underwent invasive measurement. FFR-CT measurements were performed by 2 independent analysts in a blinded manner at 2 different time points using the same CCTA dataset. For 12 lesions that showed an FFR \(\geq 0.8\), the coefficient of variation between the first and second FFR-CT measurements (interval: 51±11 days) was 3.4% (95% CI: 1.4–4.6), and the coefficient of variation between the first and second invasive FFR measurements (interval: 29±8 days) was 2.7% (95% CI: 1.8–3.3). Even for the lesions with FFR values in the range of 0.70–0.90, the coefficient of variation for FFR-CT and FFR was 3.3% (95% CI: 1.5–4.3) and 3.6% (95% CI: 2.3–4.6), respectively, indicating high reproducibility of both methods.\(^5\)\(^8\)

### 13.5 Diagnostic Performance

The DISCOVER-FLOW study compared the performance of CCTA+FFR-CT (cutoff value: 0.8) with that of CCTA alone for diagnosis of \(\geq 50\%\) stenosis in 159 vessel segments of 103 patients (at 4 centers in 3 countries) who had known or suspected coronary heart disease and underwent CCTA/invasive coronary angiography/standard invasive FFR measurement, using the result obtained by invasive FFR (cutoff value: 0.8) as the reference. For FFR-CT vs. CCTA, the respective diagnostic accuracy was 84.3% and 58.5%, sensitivity was 87.9% and 91.4%, specificity was 82.2% and 39.6%, positive predictive value was 73.9% and 46.5%, and negative predictive value was 92.2% and 88.9%. Based on the area under the curve (AUC) determined by receiver-operator characteristics (ROC) analysis, diagnostic performance was significantly better with FFR-CT than CCTA (0.90 vs. 0.75, \(P=0.001\)). Although FFR-CT displayed slight underestimation (0.022±0.116, \(P=0.016\)), there was a strong correlation between FFR-CT values and invasive FFR values (\(r=0.717, P<0.001\)).\(^5\)\(^9\)

Secondary performance was evaluated in 42 patients (66 lesions) in whom the CACS (AS) was measured, including 11 patients with an AS of 101–400 and 13 patients with an AS \(\geq 400\). When the patients were divided into 3 groups based on the AS (0–100, 101–400, and \(\geq 400\)), the diagnostic accuracy per patient was respectively 82.5%/95.0%/100%; and that for coronary artery was 77.8%/100%/100%. Accordingly, FFR-CT was beneficial for diagnosing stenosis associated with severe calcification.\(^5\)\(^8\)

The DeFACTO study\(^5\)\(^8\) prospectively evaluated the diagnostic performance of FFR-CT in 252 patients with stable angina enrolled at 17 centers in 5 countries who underwent invasive coronary angiography (including invasive FFR for 3 vessels) within 60 days of CCTA (\(\geq 64\) row), investigating the hypothesis that the addition of FFR-CT to CCTA would improve the diagnostic performance for detecting significant stenosis (\(\geq 50\%\)). The results showed a significant reduction of invasive FFR (cutoff value: 0.8) in 137 patients, and the sensitivity, specificity, and positive predictive value of CCTA+FFR-CT (cutoff value: 0.8) relative to invasive FFR (cutoff value: 0.8) was 90%, 54%, and 67%, respectively. However, the diagnostic accuracy of CCTA+FFR-CT was only 73% (95% CI: 67–78%) and the lower limit of the 95% CI did not exceed 70%, which was an unexpected result because the diagnostic accuracy of CCTA alone was 64% (95% CI: 58–70%).\(^5\)\(^8\)

Using updated FFR-CT analysis software based on data from these 2 studies, the NXT study\(^5\)\(^8\) compared CCTA+FFR-CT (cutoff value: 0.8) and CCTA alone for detecting \(\geq 50\%\) stenosis, with standard invasive FFR (cutoff value: 0.8) as the reference, in 254 patients who had 30–90% stenosis on CCTA and were enrolled at 10 centers in 9 countries, including Japan. Reproducibility of CCTA+FFR-CT (described above) was also evaluated and secondary analysis of patients with severe coronary artery calcification was performed. The per-patient diagnostic accuracy of CCTA+FFR-CT and CCTA alone was 81% and 53%; the sensitivity was 86% and 94%, specificity was 79% and 34%, positive predictive value was 65% and 40%, and negative predictive value was 93% and 92%, respectively. The AUC of the ROC analysis curve was 0.9 (95% CI: 0.87–0.94) and 0.81 (95% CI: 0.76–0.87), respectively, and the diagnostic performance of CCTA+FFR-CT was significantly higher (\(P=0.0008\)).\(^5\)\(^6\)

In a secondary analysis, 214 patients who had their AS evaluated were divided into quartiles (by patient: 302±468 [0–3,599]; by coronary artery: 95±172 [0–1,703]), and it was found that the diagnostic accuracy, sensitivity, and
specificity of FFR-CT did not differ among the quartiles in both “per-patient” and “per coronary artery” analyses, with the diagnostic accuracy and specificity of FFR-CT being superior to those of CCTA alone. In the “per-patient” evaluation, when patients were divided into a high AS group (Q4: AS=416–3,599) and a low/intermediate AS group (Q1–Q3: AS=0–415), the AUC of the ROC analysis curve did not differ significantly between groups (AUC: 0.86 vs. 0.92; P=0.45). Similarly in the “per coronary artery” evaluation, the AUC of the ROC analysis curve for the high AS group (Q4: AS=121–1,703) and the low/intermediate AS group (Q1–Q3: AS=0–120) showed no significant difference (AUC: 0.91 vs. 0.95; P=0.65). In the high AS group, FFR-CT was superior to CCTA alone for diagnosing ischemia on a “per coronary artery” basis (AUC: 0.91 vs. 0.71; P=0.004), but no significant difference was noted on a “per-patient” basis (AUC: 0.86 vs. 0.72, P=0.09). Post-hoc analysis of 57 Japanese patients enrolled in that study was also performed, revealing that CCTA+FFR-CT had significantly higher diagnostic accuracy than CCTA alone (74% vs. 47%, P=0.001). In addition, analysis of 47 Japanese patients (after excluding those with an AS >1,000, indicating severe calcification) showed a diagnostic accuracy of 83% and specificity of 76% for CCTA+FFR-CT, which were comparable to the results from the main NXT study (Figure 12).

### 13.6 Impact on Diagnosis, Treatment Planning, Cost, and Quality of Life

Douglas et al investigated whether FFR-CT was useful for selecting patients who required invasive coronary angiography (PLATFORM study). Patients with an intermediate level of risk who had new onset chest pain were enrolled prospectively, and patients in the first cohort (Cohort 1) were divided into those scheduled for noninvasive diagnostic procedures (CCTA, stress ECG, stress echocardiography, SPECT or MRI) (Group 1A) and those scheduled for invasive coronary angiography (Group 1B) according to routine clinical practice. After testing was done, the patients were treated according to the results and followed for 1 year. Enrollment of patients in the next cohort (Cohort 2) was carried out after completing enrollment in Cohort 1. The patients in Cohort 2 were divided into those scheduled for noninvasive diagnostic procedures (Group 2A) and those scheduled for invasive coronary angiography (Group 2B) according to routine practice. CCTA was also performed, which was not necessarily planned for all patients, and FFR-CT (cutoff value: 0.80) was added for lesions with ≥30% stenosis in vessels with a diameter ≥2 mm. Treatment was based on the results of CCTA+FFR-CT and follow-up was performed for 1 year.

Group 1B (n=187) and Group 2B (n=193) were scheduled for invasive coronary angiography, which revealed that 137 patients (73%) and 24 patients (12%), respectively, did not have occlusive coronary lesions. The difference in the frequency of unnecessary procedures between the 2 groups was 61% (95% CI: 53–69, P=0.0001). That is, 61% of the invasive coronary angiography procedures done in Group 1B could be avoided by performing FFR-CT. The average cumulative radiation exposure was 9.4±4.9 mSv in Group 1B and 9.9±8.7 mSv in Group 2B, so it was similar (P=0.20). Group 1A (n=100) and Group 2A (n=104) were initially scheduled for noninvasive examinations. The number of patients without occlusive coronary artery lesions on subsequent invasive coronary angiography was 6 (6%) and 13 (13%), respectively, showing no significant difference between these 2 groups (P=0.95). These findings indicate that FFR-CT is safe and effective for selecting patients who require invasive coronary angiography, and also that if FFR-CT is normal, it is highly likely invasive coronary angiography will not detect any obstructive lesions.

In a secondary analysis of the cost-effectiveness and impact on QOL, assessment of the patients scheduled for invasive coronary angiography showed 32% of average cost reduction (for diagnostic tests, invasive procedures, hospitalization, and medications during 90 days of follow-up) in Group 2B (CCTA+FFR-CT) compared with Group 1B (standard management) (Group 1B: 10,734 USD vs. Group 2B: 7,343 USD; P=0.0001), but the difference in cost was not significant among the patients scheduled for noninvasive examination (Group 1A: 2,137 USD vs. Group 2A: 2,679 USD; P=0.26). QOL improved in all groups, and among the patients scheduled for noninvasive examination, there was a trend towards better QOL in the CCTA+FFR-CT group (Group 2A) compared with the standard management group (Group 1A).

After follow-up for 1 year (n=581), MACE occurred in 4 patients scheduled for invasive coronary angiography (2 each in Groups 1B and 2B), while only 1 patient had a major cardiovascular event among those scheduled for noninvasive examination (standard management: Group 1A). Among patients scheduled for invasive coronary angiography, the total cost was significantly lower in Group 2B (CCTA+FFR-CT) than in Group 1B (standard management) (Group 1B: 12,145 USD vs. Group 2B: 8,127 USD; P=0.0001). Among patients scheduled for noninvasive examination, there was no significant difference in the total cost between Group 2A (CCTA+FFR-CT) and Group 1A (standard management) (Group 1A: 2,579 USD vs. Group 2A: 3,049 USD; P=0.82) if the cost of FFR-CT was assumed to be zero, but the total cost was significantly higher in Group 2A (3,223 USD) when the cost was assumed to be equivalent to that of CCTA (P<0.01). QOL showed similar improvement in both the patients undergoing CCTA+FFR-CT and those receiving standard management. Among patients scheduled for noninvasive examination, however, the 5-item EuroQOL scale score showed greater improvement in those receiving CCTA+FFR-CT than in those receiving standard management (mean change: 0.12 vs. 0.07, P=0.02).

Outside the USA, the National Institute for Health and Care Excellence (NICE) of the UK reported in February 2017 that FFR-CT is safe and has a high diagnostic performance, and its use helps to avoid invasive testing. It was also stated that £214 could be saved per patient. In Japan, assuming that the medical expenses of all 254 patients in the NXT study were covered by the Japanese healthcare system, costs would be lower for the patients undergoing CCTA+FFR-CT compared with those receiving standard management (7,222 USD equivalent vs. 10,360 USD equivalent) at 1 year, with a lower incidence of cardiac events (1.9% vs. 2.4%).

### 13.7 Current Situation in Japan

In Japan, HeartFlow FFR-CT was covered by the national health insurance scheme in December 2018, but only a limited number of centers are eligible.
Further evidence is accordingly required. Restoration of flow by PCI and revascularization are indicated by noninvasive CT. However, the clinical studies conducted so far have not been able to determine whether or not myocardial ischemia and treatment of chronic coronary heart disease. LGE MRI clearly delineates the location and extent of myocardial infarction. It is useful for examining myocardial viability, and for detecting right ventricular infarction, the 2007 ACC/AHA guideline indicates that it is safe to perform MRI at 1.5 or 3 T immediately after implantation of a DES, and there have been no reports of problems with other types of coronary stents. In addition, there have been no problems when MRI was performed postoperatively in patients with cardiomyopathy or for detecting asymptomatic subendocardial infarction and subendocardial ischemia. Therefore, according to the criteria of the JCS 2018 Guideline on Diagnosis of Chronic Coronary Heart Diseases, the presence or absence of myocardial ischemia from cardiac CT images in whom it is difficult to determine the extent to which CCTA+FFR-CT changes treatment strategies in comparison with CCTA alone.

### 13.8 Future Prospects

This section has primarily described the current status of HeartFlow FFR-CT, for which regulatory approval has been granted. Currently (as of December 2018), the ADVANCE study is underway with a target of 5,000 patients from around the world, and its primary endpoint is the extent to which CCTA+FFR-CT changes treatment strategies in comparison with CCTA alone. In addition to HeartFlow FFR-CT, various attempts have been made to estimate the standard invasive FFR from CCTA data using different algorithms. It would be extremely useful to be able to determine whether or not myocardial ischemia and revascularization are indicated by noninvasive CT. However, the clinical studies conducted so far have not allowed sufficient comparison with myocardial scintigraphy, the cornerstone of evaluation of myocardial ischemia. Further evidence is accordingly required. Recommendations and levels of evidence for FFR-CT are shown in Table 36.

### 14. Magnetic Resonance Imaging (MRI)

Cardiac MRI shows high diagnostic performance for evaluating myocardial infarction and myocardial ischemia, which are particularly important factors in the diagnosis and treatment of chronic coronary heart disease. LGE MRI clearly delineates the location and extent of myocardial infarction. It is useful for examining myocardial viability and for detecting right ventricular infarction, as well as for detecting asymptomatic subendocardial infarction and small infarcts. Stress myocardial perfusion MRI is useful for investigating the presence and extent of myocardial ischemia and can be used to clearly delineate subendocardial ischemia because of its high spatial resolution. Furthermore, a multicenter study and meta-analysis demonstrated better performance of stress myocardial perfusion MRI for diagnosing significant coronary stenosis compared with stress myocardial SPECT. There is also accumulating evidence about the usefulness of LGE MRI and stress myocardial perfusion MRI for predicting the prognosis of patients with coronary heart disease. The problems with cardiac MRI are the need for a long examination time when ≥2 imaging modalities are combined, and the possibility that sufficient image quality and diagnostic performance may not be achieved through inadequate knowledge and/or techniques for examination and imaging.

### 14.1 Characteristics and Technical Aspects

#### 14.1.1 Advantages and Disadvantages

MRI is a diagnostic imaging method that involves the application of a strong magnetic field and measurement of changes in the alignment of protons in body water and fat. It is also characterized by no exposure to radiation. ECG-gated imaging of the heart is performed with breath-holding or with respiratory synchronization to minimize movement caused by the heart beating and respiratory excursion. Although the imaging time for cardiac MRI was initially quite long, innovations such as parallel imaging and compressed sensing have allowed high-speed imaging. MRI has a higher spatial resolution than radionuclide imaging and has the advantage of being able to diagnose subendocardial infarction and subendocardial ischemia. Thanks to high contrast resolution between lesions and normal tissue, LGE MRI can delineate infarcted myocardium and fibrosis more clearly than contrast-enhanced CT. Because MRI is not affected by calcification or bone and there is no limitation of the visual field by the lungs, it is possible to obtain dynamic images in any desired cross-sectional view, and the reproducibility and objectivity of findings are also excellent.

The disadvantages of cardiac MRI are as follows. The scanner is more expensive than that for echocardiography, it cannot be performed at bedside, some imaging methods require a skilled technologist, and the imaging time is longer than for MDCT. Moreover, stress myocardial perfusion MRI requires pharmacological stress to be applied while the patient is in the MR unit, which is probably an obstacle to its widespread use.

With regard to the feasibility of undertaking cardiac MRI after implantation of various devices, the 2007 ACC/AHA guideline indicates that it is safe to perform MRI at 1.5 or 3 T immediately after implantation of a DES, and there have been no reports of problems with other types of coronary stents. In addition, there have been no problems when MRI was performed postoperatively in patients with
prosthetic heart valves. In relation to pacemakers and ICDs, an increasing number of devices are reported to be conditionally compatible with MR. However, adequate attention needs to be paid to device-specific standards and conditions for implementation of MRI.

### 14.1.2 Safety of Gadolinium-Based Contrast Media

Administration of a contrast agent is necessary for LGE MRI and stress myocardial perfusion MRI. NSF is a serious adverse reaction to gadolinium-based contrast media, in which pain, swelling, and hardening of the skin occur relatively acutely in patients with renal failure, particularly those on dialysis, and it can progress to cause contractures of the joints. In a gadolinium-based contrast medium, gadolinium is bound to a chelating agent. After intravenous administration, the contrast medium is filtered by the renal glomeruli and rapidly eliminated from the body if renal function is normal. However, the contrast medium remains in the body for an extended period in patients with renal failure, and it is thought that gadolinium is released from the chelator and deposited in the skin and other organs where it provokes fibrosis. Contrast agents for MRI are classified as linear or macrocyclic. The bond between gadolinium and the chelator is more stable in macrocyclic contrast agents than in linear agents, and NSF occurs more frequently when a linear contrast agent (with less stability) is administered to dialysis patients. As such, a macrocyclic contrast agent with high stability should be used when contrast-enhanced cardiac MRI is performed. The ESUR guidelines recommend that patients with impaired renal function (stage 4–5 CKD) who require contrast-enhanced MRI should receive a minimum dose of a macrocyclic contrast agent (≤0.1 mmol/kg) and that the procedure should not be repeated within 7 days.

### 14.2 Imaging Methods

#### 14.2.1 Assessment of Cardiac Morphology and Function: Cine MRI (Figure 13)

Cine MRI is not influenced by bone or air, and can capture moving images of the heart with high spatial resolution in any desired projection. Precise measurement of left ventricular function can be performed, even in patients with myocardial infarction who have left ventricular deformity and abnormal wall motion. Cine MRI is currently the most accurate diagnostic procedure for assessment of cardiac function and regional wall motion. In addition, measurement of left ventricular function and cardiac mass by MRI is highly reproducible and the results show minimal variation, so it is suitable for assessing changes over time and the response to treatment. Recently, tracking-based analysis of cine MRI images from routine cardiac examination has enabled quantitative assessment of myocardial strain, and global strain determined from cine MRI is reported to be a better predictor of the prognosis after myocardial infarction than LVEF or infarct mass.

#### 14.2.2 Diagnosis of Myocardial Infarction: LGE MRI (Figure 14)

LGE MRI is currently the most accurate imaging modality for myocardial infarction. Imaging of LGE MRI approximately 10 min after intravenous injection of a gadolinium-based contrast medium shows a high signal in infarcted myocardium from the acute to chronic phases, allowing the presence and extent of myocardial infarction to be examined. The advantages of LGE are that the contrast-enhanced area corresponds well with the pathological infarct zone on TTC (2,3,5-Triphenyl tetrazolium chloride) staining from the acute to the chronic phase and that its high spatial resolution allows examination of right ventricular infarction and subendocardial infarction, which cannot be assessed by radionuclide imaging. In an animal study based on histopathologic comparison, the diagnostic sensitivity of LGE MRI for subendocardial infarction was 92%, which was higher than that of...
14.2.3 Diagnosis of Myocardial Ischemia: Stress Myocardial Perfusion MRI (Figure 15)

In patients with angina pectoris, the goal of performing revascularization for coronary stenosis is to eliminate myocardial ischemia. However, the morphological severity of stenosis on coronary angiography or CCTA does not always correspond with the extent of functional stenosis affecting blood flow. In order to improve prognosis by performing PCI, it is important to assess the presence or absence of myocardial ischemia and the extent of the ischemic region. To perform myocardial perfusion MRI, bolus infusion of a gadolinium-based contrast medium is combined with dynamic MRI of the myocardium, allowing the myocardial blood flow distribution to be assessed from the first-pass myocardial dynamics of the contrast medium. A coronary vasodilator (e.g., adenosine, ATP, or dipyridamole) is administered to identify myocardial hypoperfusion associated with coronary artery stenosis. Because of its high spatial resolution, stress myocardial perfusion MRI can clearly depict subendocardial ischemia. Previous studies based on comparison with significant coronary artery stenosis detected by coronary angiography have indicated that stress myocardial perfusion MRI shows significantly better diagnostic performance than stress myocardial SPECT.

14.2.4 Diagnosis of Coronary Artery Stenosis: Coronary MRA (Figure 16)

Some advantages of coronary MRA are not shared by CCTA, including absence of radiation exposure, no need for contrast agents, and no influence of severe coronary artery calcification. Whole-heart coronary MRA is a method for obtaining 3-dimensional images of the entire heart with respiratory synchronization and ECG gating. Coronary MRA using a 1.5-T MRI unit is inferior to CCTA in terms of spatial resolution and imaging time, but coronary MRA is the method of first choice for patients with coronary artery anomalies, coronary artery aneurysm caused by Kawasaki disease, and renal failure. In patients with severe coronary calcification, the specificity and negative predictive value of CCTA are compromised, whereas calcification has little influence on coronary MRA and diagnosis of stenosis is still possible. On the other hand, sites where metal stents have been implanted cannot be visualized, because of metal artifacts, so evaluation of stent restenosis cannot be performed with coronary MRA. MRA is expected to be useful in screening for coronary heart disease because it does not involve radiation exposure and does not require the administration of contrast medium (noncontrast testing). There is no evidence for the usefulness of coronary MRA in asymptomatic patients, however. It should be noted that the positive predictive value of coronary MRA tends to be low in persons undergoing screening (who have a low pretest probability) and conversely many false-positive results may occur in such populations, leading to an increase in unnecessary CCTA and coronary angiography.

14.2.5 Blood Flow Measurement: Phase-Contrast Cine MRI

Phase-contrast cine MRI is used to measure blood flow by MRI. Phase-contrast cine MRI provides phase images in addition to conventional magnitude images, and the signals in the phase images are proportional to blood flow velocity. This method is sometimes used to measure blood flow in...
the coronary arteries and bypass grafts for diagnosis of coronary heart disease.619,620

When phase-contrast cine MRI is used to measure coronary sinus blood flow at rest and after administration of a coronary vasodilator, the global blood flow reserve of the entire left ventricular myocardium can be determined noninvasively, which previously could not be evaluated without performing myocardial blood flow PET.621 Recent reports from Western countries have indicated that reduction in global blood flow reserve on phase-contrast cine MRI is a prognostic factor that is independent of the presence and extent of ischemia and LGE, and it is highly useful for risk stratification of patients with coronary heart disease.422,623

14.3 Significance in the Diagnosis of Chronic Coronary Heart Disease

14.3.1 Evaluation of Myocardial Viability

LGE MRI can clearly delineate myocardial infarction from the acute to the chronic phase, and the transmural extent revealed by this modality strongly correlates with restoration of myocardial contractility. Accordingly, LGE MRI is useful for deciding treatment strategies, such as the indications for revascularization. Among cardiac segments with regional wall motion abnormalities, the rate of functional restoration after revascularization in patients with chronic coronary heart disease was 78% for segments with a transmural extent of 0%, decreasing to 60% for an extent of 1–25%, 42% for 26–50%, 10% for 51–75%, and 1.7% for 76–100%.624 In addition, LGE MRI can clearly show whether or not myocardial necrosis exists in patients with myocardial infarction, with the necrosis area accounting for almost 25% of the left ventricular myocardium. In ischemic cardiomyopathy, LGE MRI shows high-resolution images that depict myocardial fibrosis and can accurately distinguish ischemic cardiomyopathy due to coronary heart disease from nonischemic cardiomyopathy on the basis of myocardial imaging patterns.625 In ischemic cardiomyopathy, LGE involving the (sub)-endocardium and continuous in its epicardial direction is recognized. On the other hand, approximately 30% of patients with nonischemic cardiomyopathy show mid-wall LGE, which is closely associated with the risk of arrhythmic death.626

14.3.2 Diagnosis of Myocardial Ischemia

Stress myocardial perfusion MRI can identify regions of myocardial ischemia associated with coronary stenosis, and it is not only possible to diagnose coronary stenosis in patients with angina pectoris, but also to assess restenosis after PCI. MRI has better spatial resolution than radionuclide imaging and is superior for diagnosis of subendocardial ischemia and multivessel disease. Using significant stenosis on coronary angiography as the gold standard, research has indicated that stress myocardial perfusion MRI shows superior diagnostic performance to SPECT.615 In a meta-analysis based on comparison with coronary angiography combined with FFR, the performance of stress myocardial perfusion MRI for detection of coronary artery lesions was significantly better than that of stress myocardial SPECT, and almost equivalent to stress myocardial perfusion PET.627

14.3.3 Prediction of the Prognosis

Evidence is being accumulated with regard to prediction of the prognosis by stress myocardial perfusion MRI and LGE MRI. A meta-analysis performed by Lipinski et al showed that the annual incidence of events (cardiac death or myocardial infarction) was 0.8±0.7% in patients who were negative for ischemia on stress myocardial perfusion MRI, but was 4.9±3.1% in those positive for ischemia and the odds ratio was 6.5 (95% confidence interval [CI]: 4.4–9.6).628 In addition, the annual incidence of events was 1.4±1.0% in patients without infarction or fibrosis on LGE MRI and 4.6±4.0% in patients positive for late enhancement, with an odds ratio of 3.8 (95% CI: 2.6–5.7). Thus, the annual incidence of events is <1% in patients without ischemia on stress myocardial perfusion MRI, and stress cardiac MRI may have similar value to cardiac radionuclide imaging for risk stratification of patients with suspected coronary heart disease.

The CE-MARC study was a prospective comparison of diagnostic performance between cardiac MRI and myocardial SPECT, and it also compared the usefulness of these 2 modalities for predicting the risk of MACE.629 Among the 628 patients who underwent both cardiac MRI and myocardial SPECT, 104 developed MACE, and univariate analysis showed that the hazard ratio for predicting MACE by cardiac MRI and myocardial SPECT was 2.77 (P<0.001) and 1.62 (P=0.014), respectively. Multivariate analysis showed that only cardiac MRI was a significant prognostic factor, and these results support the importance of selecting cardiac MRI for risk stratification of patients with suspected coronary heart disease.

Revascularization is known to improve prognosis more than medical therapy when stress myocardial SPECT shows that ischemic myocardium exceeds 10% of the total myocardial volume.229 A recent study revealed that the ischemic myocardial volume threshold was 9% for performing revascularization based on stress myocardial perfusion MRI, and that patients with an ischemic myocardial volume <9% who did not undergo revascularization had a similar prognosis to those without ischemia.630

14.3.4 Coronary MRA

The greatest advantage of coronary MRA is that it can exclude the diagnosis of coronary stenosis in patients who have chronic coronary heart disease without exposing them to radiation. Disadvantages of coronary MRA include the longer imaging time, lower spatial resolution compared with CT, and difficulty in evaluating the lumen of coronary stents. In 2001, a multicenter study of gradient echo coronary MRA using catheter coronary angiography as the reference showed good sensitivity and specificity of MRA for left main trunk disease and triple-vessel disease. For lesions in the entire coronary artery tree, the sensitivity of MRA was high (93%), but its specificity was low (42%).631 Coronary MRA imaging has since progressed to whole-heart coronary MRA using steady-state protocols,632 and a multicenter Japanese study based on comparison with catheter coronary angiography showed improved diagnostic performance of MRA, with a sensitivity of 87%, specificity of 71%, positive predictive value of 71%, and negative predictive value of 87%.633

The 3-T MRI units provide images with a better signal-to-noise ratio than 1.5-T units, and allow acquisition of higher-quality coronary MRA images. A meta-analysis showed that 3 T coronary MRA has a sensitivity of 93% and specificity of 83%,634 which means its diagnostic potential is approaching that of 64-row CT. Recent advances in
Coronary angiography (CAG) can evaluate the presence, site, distribution, and extent (severity) of stenotic lesions or dilated lesions in the coronary arteries throughout the entire coronary artery tree. CAG is the best option for detailed assessment of coronary artery anatomy. Historically, CAG was initiated in 1958 with the invention of the so-called semiselective technique by Sones, in which a catheter was advanced to the left and right sinuses of Valsalva and 20–30 mL of contrast medium was injected over 3–6 s. In 1967, a catheter with modified tip shapes for left and right CAG were developed by Judkins, and the percutaneous femoral approach was established.

After that, the Sones approach via brachial arteriotomy and the Judkins approach with percutaneous femoral artery puncture were used for selective CAG, but today all catheterization is done via percutaneous femoral approach. CAG is the best choice for assessing the detailed anatomy of the coronary arteries, but it does not directly evaluate the functional severity of coronary artery lesions or associated physiological abnormalities. When performing CAG, the severity of stenosis is usually evaluated by comparison with a nearby contrast-enhanced “normal” vessel segment. However, the so-called normal vessel may be affected by arteriosclerosis, leading to underestimation of stenosis in many cases. Moreover, assessment of the absolute minimum vessel diameter does not help to define the extent of abnormality of the luminal diameter, because the appropriate measurements are obtained with angiographical equipment.

Recommendations and levels of evidence for MRI are shown in Table 37.

### 14.4 Future Challenges

The indications for CAG are determined by comprehensive evaluation of many factors, such as the patient’s age, activities of daily living, comorbidities, and expectations. Accordingly, it is difficult to establish uniform criteria for the indications. However, it is generally considered appropriate to perform CAG in patients who have angina that interferes with daily activities or who are in the high-risk or sometimes moderate-risk category based on noninvasive tests, provided they are refractory to drug therapy. It is also considered reasonable to perform CAG in patients with atypical symptoms who require a definitive diagnosis if a stress test has failed to provide a diagnosis. Defining standard indications is important for preventing the overuse of CAG. One of the major reasons for performing CAG is to determine the indications for invasive therapies such as PCI and CABG. It is established that PCI or CABG improves angina pectoris, regardless of the number of vessels involved. It is thus important to distinguish patients with angina pectoris from asymptomatic persons.

### 15. Coronary Angiography

#### 15.1 Indications

The indications for CAG should be determined by comprehensive evaluation of many factors, such as the patient’s age, activities of daily living, comorbidities, and expectations. Accordingly, it is difficult to establish uniform criteria for the indications. However, it is generally considered appropriate to perform CAG in patients who have angina that interferes with daily activities or who are in the high-risk or sometimes moderate-risk category based on noninvasive tests, provided they are refractory to drug therapy. It is also considered reasonable to perform CAG in patients with atypical symptoms who require a definitive diagnosis if a stress test has failed to provide a diagnosis. Defining standard indications is important for preventing the overuse of CAG. One of the major reasons for performing CAG is to determine the indications for invasive therapies such as PCI and CABG. It is established that PCI or CABG improves angina pectoris, regardless of the number of vessels involved. It is thus important to distinguish patients with angina pectoris from asymptomatic persons.

### 15.2 Diagnostic Performance

CAG is the best choice for assessing the detailed anatomy of the coronary arteries, but it does not directly evaluate the functional severity of coronary artery lesions or associated physiological abnormalities. When performing CAG, the severity of stenosis is usually evaluated by comparison with a nearby contrast-enhanced “normal” vessel segment. However, the so-called normal vessel may be affected by arteriosclerosis, leading to underestimation of stenosis in many cases. Moreover, assessment of the absolute minimum vessel diameter does not help to define the extent of abnormality of the luminal diameter, because the appropriate measurements are obtained with angiographical equipment.

### Table 37. Recommendations and Levels of Evidence for MRI for the Diagnosis of Chronic Coronary Heart Disease

<table>
<thead>
<tr>
<th>MRI Type</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cine MRI (chronic coronary syndrome with heart failure)</td>
<td>IIA</td>
<td>C</td>
<td>C1</td>
<td>V</td>
</tr>
<tr>
<td>LGE MRI (differentiation between ischemic cardiomyopathy due to chronic coronary syndrome and nonischemic cardiomyopathy)</td>
<td>IIA</td>
<td>B</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>LGE MRI (assessment of myocardial viability)</td>
<td>IIA</td>
<td>C</td>
<td>C1</td>
<td>IVa</td>
</tr>
<tr>
<td>Stress myocardial perfusion MRI (assessing myocardial ischemia and evaluating indication of revascularization)</td>
<td>IIA</td>
<td>B</td>
<td>B</td>
<td>II</td>
</tr>
<tr>
<td>Coronary MRA (exclusion of coronary artery disease in the presence of chest pain syndrome)</td>
<td>IIB</td>
<td>C</td>
<td>C1</td>
<td>IVb</td>
</tr>
<tr>
<td>MRA (screening of coronary artery disease in asymptomatic population)</td>
<td>III</td>
<td>C</td>
<td>C2</td>
<td>VI</td>
</tr>
</tbody>
</table>

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.
luminal diameter varies depending on the site of the lesion. It is also difficult to estimate the luminal area of a tortuous vessel. This problem is evident immediately after PCI.

Issues with reproducibility are also inevitable when evaluating coronary lesions, particularly when a visual assessment is performed. To overcome this limitation, several methods of quantitative CAG have been developed, including edge detection and video densitometry. Although reproducibility and objectivity are markedly improved by quantitative CAG, accuracy is inferior at sites with a luminal diameter ≤1 mm because of problems with resolution. When assessing the functional significance of lesions, a range of about 1 mm in luminal diameter is of vital importance. CAG provides a view of the borders of the vessel lumen and does not provide information on the nature of the coronary artery wall or the severity of atherosclerosis. To assess the properties of the coronary artery wall, the extent of atherosclerosis, and the true luminal diameter, imaging methods that can evaluate the vessel walls, such as coronary artery IVUS (described later), should be combined with angiography.

### 15.3 Results and Their Significance

CAG is the best method for visually demonstrating the presence of coronary artery stenosis and coronary artery spasm, although it has limitations for diagnosis of coronary heart disease, as described in the previous section. Clarifying the presence of coronary heart disease can help to determine the need for coronary revascularization and drug therapy.

#### 15.3.1 Assessment of Severity

Assessment of the severity of coronary heart disease is the most important use for CAG, because assessment of severity allows stratification of the vital prognosis. The prognostic factors that are currently known to be obtained from CAG and left ventriculography include ≥50% stenosis of the left main trunk, as well as the presence of triple-vessel disease with left heart dysfunction (LVEF <50%). In patients with these findings, CABG has been shown to improve the vital prognosis. The SYNTAX score is an indicator of the complexity of coronary lesions on CAG, and it has been reported to be useful for selecting CABG or PCI for patients with severe coronary heart disease such as triple-vessel or...
left main trunk disease.\textsuperscript{645,646}

\subsection*{15.3.2 Determination of Indications for Treatment}
Despite the fact that CCTA has provided new options for evaluation of coronary lesions, CAG is still essential for examining the anatomical suitability of a patient for invasive treatment (PCI or CABG). Information that can be obtained from CAG, such as the site of lesion, severity of stenosis, vessel diameter, lesion length, presence/absence of thrombus, and presence/absence of calcification, is important for predicting the initial success of PCI and long-term outcomes. The presence or absence of peripheral coronary artery lesions is also important to determine when deciding the indications for CABG.

\subsection*{15.3.3 Assessment of the Effect of Treatment}
CAG is often performed to detect restenosis after PCI, to assess the patency of coronary artery bypass grafts, or to investigate regression of coronary lesions. Although QCA has played a significant role in clinical studies evaluating improvements of devices, it has often been pointed out that a clinical index should be used in such studies rather than an imaging index. In particular, the clinical significance of CAG for judging the effects of treatment has not been clarified. It has also been reported that performing follow-up CAG adds to the rate of repeat PCI.\textsuperscript{647} Accordingly, routine follow-up CAG, which was conventionally performed after PCI, is not recommended for patients without symptoms or ischemic findings. Likewise, performing CAG after CABG to evaluate graft patency is not recommended in the absence of symptoms or ischemic findings.

\subsection*{15.4 Complications}
The incidence of death associated with CAG does not exceed 0.2\%, and the incidence of major complications (stroke, myocardial infarction, and hemorrhage) does not exceed 0.5\%.\textsuperscript{648} The risk of complications is higher when a decrease in blood pressure is noted on exercise testing or ST depression is widespread and prominent together with a low heart rate.\textsuperscript{649} Other risk factors that have been identified include left main trunk disease, severe triple-vessel disease, left heart dysfunction, critical aortic stenosis, and advanced age.\textsuperscript{649}

In recent years, the incidence of serious complications has been decreasing due to miniaturization of catheters, improvement of catheterization techniques, and better treatment of complications. For example, myocardial infarction caused by coronary artery dissection was generally a serious complication leading to emergency CABG and death, but it is now possible to avoid infarction by rapid deployment of a stent. In addition, CAG via radial artery puncture has been reported to result in approximately 70\% fewer major bleeding complications and approximately 30\% fewer major cardiovascular complications (death, myocardial infarction, and stroke) compared with femoral artery puncture.\textsuperscript{650} Moreover, anaphylactic shock due to ionic contrast medium was not a rare event, but use of nonionic contrast media has dramatically reduced the incidence of shock. Although thrombus formation associated with nonionic contrast media has been pointed out in Western countries, it does not seem to be a major problem in Japanese patients.

It has also been pointed out that CAG can lead to performance of unnecessary PCI and CABG. This issue has long been known and has been given the name of the oculostotic reflex, which means that nonindicated use of CAG leads to an increase in PCI and CABG procedures without obvious clinical value. Therefore, CAG should only be performed according to appropriate indications.

\section{16. Coronary Spasm Provocation Testing}
Coronary spasm provocation testing is performed by combining coronary artery imaging with selective intracoronary infusion of acetylcholine or ergonovine. It is done to confirm coronary spasm in patients with rest angina or to exclude coronary spasm in patients with atypical chest pain, and is also sometimes performed in patients with effort angina or nonacute myocardial infarction. The sensitivity and specificity of provocation testing for detection of coronary spasm are as high as 80–90\%. Sensitivity is reduced by drug therapy before stress testing and is also lower in patients with less frequent attacks. It sometimes is difficult to determine whether coronary spasm induced by this test has true clinical and pathological significance. However, patients with multivessel coronary spasm have a poor long-term prognosis. With regard to coronary spasm testing with acetylcholine, an additional indication (Ovisot® for Injection 0.1 g) was approved on August 25, 2017, and health insurance cover was officially granted for pharmacological coronary spasm testing with acetylcholine in the 2018 fiscal year.

\subsection*{16.1 Characteristics and Technical Aspects}
There are many patients with rest angina in Japan. In these patients, coronary angiography often confirms coronary spasm,\textsuperscript{651,652} but the frequency of angina attacks is not necessarily high when Holter ECG is performed. For this reason, invasive coronary spasm provocation testing with acetylcholine or ergonovine is often performed in patients with rest angina.

Typically, an acetylcholine\textsuperscript{653} or ergonovine provocation test\textsuperscript{654} is implemented. In the acetylcholine provocation test, selective intracoronary infusion of acetylcholine is performed at a dose of 20–100\(\mu g\). The initial intracoronary dose is smaller (20\(\mu g\)) in patients with frequent angina attacks who are considered to have highly active disease. Because hypotension and severe bradycardia may occur during a spontaneous attack, a temporary pacing electrode should be inserted into the right ventricle.

Regarding the ergonovine provocation test, there was an early report of death due to intravenous administration of a high dose of ergonovine,\textsuperscript{655} but the usefulness of this test with intracoronary administration was subsequently reported. Thus, selective intracoronary administration, which requires lower doses of ergonovine, is now widely adopted.\textsuperscript{656,657} The dose of ergonovine for intracoronary administration varies among institutions, and there is no generally accepted standard.\textsuperscript{658} However, a dose of at least 20–60\(\mu g\) for both the left and right coronary arteries is common. For safety reasons, bolus dosing should be avoided if possible and continuous infusion should be performed instead.

\subsection*{16.2 Criteria for Deciding the Indications}
Table 39 summarizes the criteria for deciding the indications for coronary spasm provocation testing with reference to
Table 39. Recommendations and Levels of Evidence for Spasm Provocation Tests

<table>
<thead>
<tr>
<th>Category</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in whom vasospastic angina is suspected based on symptoms, but who have not been diagnosed with coronary spasm by noninvasive evaluation</td>
<td>I</td>
<td>B</td>
<td>C1</td>
<td>IVa</td>
</tr>
<tr>
<td>Patients who have been diagnosed with coronary spasm by noninvasive evaluation, and in whom medical treatment is ineffective or insufficiently effective</td>
<td>Ila</td>
<td>B</td>
<td>C1</td>
<td>IVa</td>
</tr>
<tr>
<td>Patients who have been diagnosed with coronary spasm by noninvasive evaluation, and in whom medical treatment has been effective</td>
<td>IIb</td>
<td>B</td>
<td>C1</td>
<td>IVa</td>
</tr>
<tr>
<td>Patients without symptoms suggestive of vasospastic angina</td>
<td>III</td>
<td>C</td>
<td>C2</td>
<td>VI</td>
</tr>
<tr>
<td>Patients who are more likely to develop severe and potentially fatal complications of induced coronary spasm (left main trunk disease, multivessel disease including an occlusive lesion, severe cardiac dysfunction, untreated congestive heart failure, etc.)</td>
<td>III</td>
<td>C</td>
<td>C2</td>
<td>VI</td>
</tr>
<tr>
<td>Patients with ACS undergoing emergency coronary angiography</td>
<td>III</td>
<td>C</td>
<td>C2</td>
<td>VI</td>
</tr>
</tbody>
</table>

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence. (Reproduced from data in Ogawa et al. with permission.)

the indication categories in the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina (Coronary Spastic Angina) of the Japanese Circulation Society, 458–664

16.3 Significance in the Diagnosis of Chronic Coronary Heart Disease

16.3.1 Objectives of Testing

The objectives of performing a provocation test are: (1) confirmation of coronary spasm in patients with rest angina and some patients with effort angina; (2) determination of the severity of rest angina; and (3) exclusion of coronary spasm in patients with atypical chest pain.

16.3.2 Diagnostic Performance

The sensitivity and specificity of coronary spasm provocation testing is generally quite high, being in the range of 80–90%. However, coronary spasm may not be provoked in patients who have received drug therapy before testing or in patients with infrequent spasm, even if ST elevation is confirmed by Holter ECG. Also, there are diurnal variations in the frequency of coronary spasm, and attacks only occur in the early morning in some patients. Therefore, to increase the diagnostic accuracy of pharmacological coronary spasm provocation testing, it should be performed in the morning whenever possible, and drugs, such as calcium antagonists and long-acting nitrates, should be discontinued for at least 2 days before testing if possible. On the other hand, coronary spasm associated with ECG changes may be induced even in patients without history of chest pain, but the pathological significance of such spasm is difficult to judge. The pathological significance of coronary spasm without associated ECG changes and without complete or subtotal occlusion is also difficult to assess.

16.3.3 Results and Diagnostic Significance

Confirmation of coronary spasm in patients with rest angina and some patients with effort angina justifies long-term administration of nitrates and calcium antagonists as treatment for angina pectoris. It also provides information to guide treatment with other drugs, such as whether β-blockers (which can induce coronary spasm) should be administered. Regarding the severity of rest angina, patients with multivessel coronary spasm have a poor long-term prognosis. An association between occult atherosclerotic lesions and prognosis has also been shown. In such cases, the results of provocation testing may be used to guide decisions about drug doses and the duration of treatment.

Excluding coronary spasm in patients with atypical chest pain is crucial, especially in the Japanese population, because angina stemming from coronary spasm is more frequent in Japan. CCTA has become popular in recent years and has a very high negative predictive value, so excluding coronary stenosis in patients with atypical chest pain is possible without catheter coronary angiography. However, absence of coronary stenosis does not directly exclude a diagnosis of angina. It is also problematic to keep patients on long-term treatment with nitrates or calcium antagonists for atypical chest pain without a definitive diagnosis of angina pectoris. It is crucial to perform coronary spasm provocation testing in patients with atypical chest pain to determine the appropriate therapeutic strategy.

16.4 Contraindications

Pharmacological coronary spasm provocation testing is invasive and extreme caution should be exercised when deciding the indications for this test. As indicated in Table 39, pharmacological coronary spasm provocation testing should not be performed in patients who are likely to be disadvantaged by undergoing such a test, including (1) patients without symptoms suggestive of vasospastic angina; (2) patients who are more likely to develop severe and potentially fatal complications of induced coronary spasm (left main trunk disease, multivessel disease including an occlusive lesion, severe cardiac dysfunction, untreated congestive heart failure, etc.); and (3) patients with ACS undergoing emergency coronary angiography.

16.5 Complications

When coronary spasm provocation testing is performed, severe and extensive coronary spasm may be induced and the induced vasospasm may be prolonged, especially in patients with frequent attacks or multivessel coronary
spasm. As a result, hypotension, cardiogenic shock, severe arrhythmia, and cardiac arrest may occur. In such cases, immediate alleviation of coronary spasm by intracoronary infusion of a nitrate, administration of vasopressors to maintain the blood pressure, and immediate countermeasures for serious arrhythmia may be necessary. A recent investigation of complications in 17,700 patients undergoing coronary spasm provocation testing by intracoronary administration of acetylcholine or ergonovine showed that serious procedural complications had a frequency of 0.89%, including 1 death (0.006%) and 2 cases of acute myocardial infarction (0.01%).

### 17.1.1 IVUS

When IVUS is performed, ultrasound is emitted from a transducer located at the tip of the IVUS catheter, and the ultrasound waves reflected from the coronary artery wall are converted into electrical signals that provide images of the cross-sectional architecture of the vessel. IVUS can be performed by mechanical or electronic scanning. With mechanical scanning, a single transducer rotates in the catheter at high speed to construct a 360-degree image. With electronic scanning, multiple ultrasonic transducers are arranged around the circumference of the catheter tip, and ultrasound waves are generated by each transducer to provide a 360-degree image. Generally, mechanical scanning uses high-frequency ultrasound (40–60 MHz) and achieves high resolution, but images of the ultrasound waves are only 19 μm and resolution is inferior. When performing IVUS by either method, the catheter is advanced until the sensor crosses the lesion, and then motorized pull back is performed at a constant speed (0.5–1.0mm/s) to obtain cross-sectional images of the vessel.

Recently, IVUS catheters that allow high-speed pullback (9.0mm/s) and still achieve excellent resolution using high-frequency ultrasound (60 MHz) and increasing the frame rate have become more popular. IVUS generally has the advantage of achieving transmural penetration, which makes it suitable for evaluation of the entire coronary artery wall, although its resolution is inferior to that of OCT (described next).

### 17.1.2 OCT

OCT is a relatively new intravascular imaging method that uses near-infrared light at a wavelength of 1,300 nm and constructs cross-sectional images of a coronary artery by analyzing the interference between light reflected from the artery and light reflected from a mirror in the equipment. Currently, 2 types of OCT are available for clinical use: frequency domain OCT (FD-OCT; Abbott) and optical frequency domain imaging (OFDI; Terumo). With both types, depth information can be obtained instantaneously by rapidly changing the frequency of the near-infrared band, so the spatial resolution is extremely high and the imaging time is short, enabling more rapid pullback compared with IVUS. Table 40 compares the performance of IVUS, FD-OCT, and OFDI. Because the near-infrared light used in OCT is attenuated by red blood cells in the artery, imaging is performed over several seconds after a contrast agent or low-molecular-weight dextran is injected through a guiding catheter to temporarily block coronary blood flow.

### 17.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

#### 17.2.1 IVUS

The coronary artery wall has a 3-layer structure, consisting of the tunica intima, tunica media, and tunica adventitia in order from the lumen. IVUS cannot visualize the normal tunica intima, but can depict plaques in atherosclerotic lesions as local thickening of the intima. In actual observation, the boundary between the intima and the media is often unclear and the cross-sectional area of a plaque is defined as the area of the IMC, which is calculated by tracing of the media–adventitia boundary and subtracting the luminal area (intimal area + medial area). The cross-sectional area of the lumen at the site of maximal stenosis is called the minimum lumen area. Coronary plaques are classified as soft or hard according to the IVUS echo level, but the correlation of this classification with actual plaque hardness or tissue characteristics is not strong. Recently, it has become possible to predict coronary artery tissue characteristics by displaying different tissues in different conditions in the wall of the coronary artery.
colors on IVUS images using various algorithms to compare ultrasound signals with pathological data, which is known as virtual histology IVUS (VH-IVUS: Volcano), integrated backscatter IVUS (IB-IVUS: Terumo), or iMAP (Boston Scientific).654

Calcified lesions are characterized by high echo levels and acoustic shadowing, which allows identification with high sensitivity and specificity (≥90%). Plaques with attenuation despite the absence of calcification are called attenuated plaques, and are considered to be lesions associated with a higher risk of no reflow/slow flow after PCI.676.686 Recently, IVUS has been combined with a system that detects cholesterol ester-rich lipid core plaque by near-infrared spectroscopy (NIRS-IVUS, Infraredx) and this method has been applied clinically.677 If basing therapeutic strategy on tissue characterization is shown to improve the prognosis, IVUS will be increasingly used in the future.

IVUS is also useful for determining the required size and length of coronary stents before implantation. When sizing a vessel to select balloons and stents, it is important to take vascular remodeling into account, in addition to the actual coronary artery lumen. Conventionally, the outer diameter of the distal reference vessel (media–adventitia boundary) is measured by IVUS and multiplied by 0.8–0.9 to obtain the size of the stent or balloon. Use of DES with less late lumen loss has become mainstream practice, and the stent diameter is often determined from the lumen diameter. However, care is required when the lesion is associated with negative remodeling, because there is a risk of perforation if only the reference vessel diameter is used for guidance. IVUS can also provide useful information for determining stent length by assessing residual plaque proximal to the lesion and plaque in distal segments, as well as for predicting and detecting complications such as hematoma and perforation.

A number of observational studies, meta-analyses, and RCTs have recently demonstrated the clinical usefulness of IVUS-guided PCI.678.679 In particular, IVUS-guided PCI has been shown to be useful for patients with long lesions680 or chronic total occlusion.681 A meta-analysis focusing on RCTs also suggested that IVUS-guided PCI significantly reduces major cardiovascular events, particularly target vessel revascularization, compared with reliance on coronary angiography alone.682

### 17.2.2 OCT

In OCT, the coronary artery wall is clearly observed as a layered structure, with the tunica intima showing high brightness, while the tunica media shows low brightness and the tunica adventitia also shows high brightness. In addition, coronary artery plaques have specific characteristics. Fibrous plaques are depicted as regions of high intensity with indistinct boundaries. Lipid plaques are low intensity areas with diffuse borders, while calcified plaques are seen as low brightness areas with clear borders. OCT can also identify the contours of calcification, allowing for quantitative assessment of superficial calcified lesions.683 The diagnostic sensitivity and specificity of OCT for lipid plaques were reported to be 90–94% and 90–92%, respectively, with respective values of 93–96% and 97% for calcified plaques and 71–79% and 97–98% for fibrous plaques.684 Pathological studies have shown that progression of atherosclerosis leads to development of TCFA containing a pool of lipids and cholesterol crystals, with disruption of the TCFA thought to be the main underlying cause of ACS. On OCT, TCFA is defined by detection of a thin fibrous capsule (≤65 μm) with a necrotic core occupying ≥1/4 of the vessel’s circumference.685 It was reported that examination of culprit lesions of ACS by OCT showed disruption of TCFA (plaque rupture) in 43.7%, plaque erosion in 31.0%, and calcified nodules in 7.9%.686

When performing OCT-guided PCI, the diameter of the stent is determined from the distal reference lumen diameter and a stent 0.25–0.5 mm larger than the measured lumen diameter is often selected. Recently, it has been suggested that the stent size should be determined based on the outer border of the tunica media (external elastic lamina), in light of the results of the ILUMIEN III study (described below). It has also been reported that incomplete stent expansion and chronic in-stent restenosis are associated with the severity of calcification assessed by OCT at the time of PCI, as well as with the presence or absence of cracking at sites of calcification after balloon dilatation.687.688 Moreover, detection of TCFA by OCT is associated with an increased risk of no reflow/slow flow after PCI (PCI-related myocardial infarction: type 4).689.690 Thus, OCT provides useful information for optimal stenting.

Both 2-dimensional long-axis images and 3-dimensional images can be obtained by OCT. Three-dimensional imaging allows visual observation of the complex architecture of the coronary arteries and the positional relations of guidewires and other devices, and its use as a guide for PCI is increasing, especially in the treatment of bifurcation lesions.

A recent retrospective comparison of OCT-guided PCI and coronary angiography alone showed significantly lower 12-month rates of cardiac death and myocardial infarction with OCT guidance.691 The influence of OCT on selection of PCI procedures was investigated in a multicenter prospective study (ILUMIEN I), revealing that the treatment strategy was changed in 57% of patients and additional measures to optimize treatment were carried out in 27%.692 A recent multicenter randomized controlled study (ILUMIEN III) showed that OCT guidance achieved

### Table 41. Recommendations and Levels of Evidence for Use of IVUS and OCT for the Diagnosis of Chronic Coronary Heart Disease

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVUS is reasonable for assessing severity and optimizing treatment of left main coronary artery disease</td>
<td>Ila</td>
<td>B</td>
<td>B</td>
<td>III</td>
</tr>
<tr>
<td>IVUS or OCT is reasonable for assessing mechanisms of stent failure</td>
<td>Ila</td>
<td>C</td>
<td>B</td>
<td>IVb</td>
</tr>
</tbody>
</table>

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.
similar stent expansion to IVUS, with no significant difference in major cardiovascular events up to 30 days after PCI. A Japanese multicenter randomized trial (OPINION study) compared the outcome and prognosis of OCT-guided PCI with IVUS-guided PCI, revealing no significant difference in target vessel failure (target vessel-related death, myocardial infarction, or revascularization for ischemia) and demonstrating noninferiority of OCT-guided PCI to IVUS-guided PCI (P=0.042 for noninferiority). Although there is not yet as much evidence for OCT-guided PCI as for IVUS-guided PCI, increasing use of OCT with its high resolution in the diagnosis and treatment of coronary heart disease is expected in the future. Recommendations and levels of evidence for IVUS and OCT are shown in Table 41.

17.3 Future Challenges

In patients with complex lesions, combining PCI with intravascular imaging has been shown to not only improve the acute outcome but also the long-term prognosis compared with PCI based on coronary angiography alone. On the other hand, assessment of coronary artery lesions, decisions about the indications for PCI, and treatment strategies vary widely among patients. It is important to select the optimum strategy by comprehensively assessing the clinical background, the results of coronary angiography, and the findings on intravascular imaging.

18. Angioscopy

18.1 Characteristics

Angioscopy is the only procedure by which the interior of a blood vessel can be viewed directly in vivo. The angioscope is very thin (0.75 mm in diameter) and can be safely inserted into the coronary arteries, allowing the status of plaque in the arteries to be observed directly. Plaque is localized intimal thickening of a blood vessel due to atherosclerosis. Angioscopy provides a “true image,” allowing observation of the color and surface of plaques, as well as the presence of thrombus. Angioscopy is superior for detecting thrombi and yellow plaques, particularly in patients with ACS, as well as for assessing stents after placement. This technology was developed in Japan and evidence has been accumulated for Japanese patients, although little information has been obtained in other countries.

18.1.1 Yellow Plaque

Formation of a yellow plaque starts with deposition of lipids in the coronary artery wall. The deposits form a lipid core that increases in size over time. As the fibrous capsule covering the lipid core becomes thinner, the surface of the plaque develops a yellowish color. The yellowness of plaques can be graded by angioscopy (grade 0: white; grade 1: light yellow; grade 2: yellow; grade 3: dark yellow), and the yellow grade closely correlates with the thickness of the fibrous capsule in vivo. A higher yellow grade indicates more vulnerable plaque that is more likely to cause ACS. It has been demonstrated that reduction of the LDL-cholesterol level with statin therapy decreases the yellow grade and stabilizes plaques. It has also been shown by angioscopy that not all ruptured plaque causes ACS, and that asymptomatic plaque rupture can occur. The features of plaque rupture include intimal fissures, erosions, and ulceration. Angioscopy is also important for assessing the anti-atherosclerotic effect of cholesterol-lowering drugs such as statins.

18.1.2 Thrombus

Angioscopy can detect even small thrombi and is superior to IVUS or OCT in this regard. Thrombus can be classified as white thrombus (considered to be platelet-fibrin thrombus), red thrombus (mainly contains erythrocytes), and mixed thrombus (a mixture of white and red thrombus).

18.1.3 Neointima After Stent Implantation

After stenting in patients with both ACS and stable angina, angioscopy is useful for investigating whether the stent is covered by neointima in the chronic phase and whether it is free of thrombus etc. If the metal parts of the stent are completely covered by neointima and no thrombus is present, reducing the dosage or ceasing antiplatelet drugs can be considered.

The extent of neointimal coverage of stents is classified...
into 4 grades (0–3) (Figure 17). Poor neointimal coverage and thrombi are common at sites of contrast medium exudation outside the stent (peri-stent contrast staining [PSS]), which is associated with very late stent thrombosis (VLST), a problem with 1st-generation DES. The 2nd-generation DES show better neointimal coverage compared with 1st-generation DES. With 3rd-generation DES, the occurrence of thrombosis has been reduced by the thinner stent struts and other changes.

Yellow plaque at the site of a stent is associated with cardiac death, ACS, and target lesion revascularization at 1 year, whereas reduction of LDL-cholesterol with statin therapy is associated with risk reduction. Thus, angiographic assessment of the intimal coverage of stents can often provide helpful findings for early discontinuation of dual-antiplatelet therapy and for management of lipid-lowering therapy. Recommendations and evidence levels for angiography are shown in Table 42.

19. Measurement of Intracoronary Pressure and FFR

19.1 Characteristics and Technical Aspects

Coronary angiography is regarded as the standard examination for diagnosis of chronic coronary heart disease, and the angiographic severity of stenosis has been used to determine the severity of this condition and the indications for revascularization. However, anatomical information obtained from coronary angiography cannot provide accurate information on the functional severity of a stenosis.

FFR is a parameter that assesses the functional severity of coronary stenosis and can be measured during coronary angiography, and it can be used to precisely assess the hemodynamic severity of stenotic lesions. FFR is determined by measuring the intracoronary pressure using a pressure guidewire. A monorail-type catheter has also been developed for measuring intracoronary pressure and can be used to measure FFR.

The procedure for measurement of FFR is as follows. First, the pressure guidewire is calibrated outside the body. Then, it is inserted into the guiding catheter and the pressure sensor is aligned with the tip of the guiding catheter, after which the pressure of the pressure sensor is equalized with that of the guiding catheter. Intracoronary administration of a nitrate is performed to prevent coronary spasm due to guidewire insertion, and the diameter of the coronary artery is kept constant between maximal hyperemia and baseline. Next, the pressure guidewire is advanced to the distal end of the coronary artery segment for measurement and a vasodilator (adenosine, ATP, papaverine hydrochloride, nicorandil, etc.) is administered to induce myocardial hyperemia. Theoretically, the FFR values range from 0.0 to 1.0, with 1.0 representing a normal coronary artery. The FFR values indicate the extent to which blood flow in the target coronary artery is reduced by stenosis compared with the estimated flow in the absence of stenosis. For example, FFR=0.60 indicates that a stenosis has reduced coronary blood flow to 60% of normal.

Measurement of the intracoronary pressure is performed by using a pressure guidewire. A typical pressure guidewire has almost the same shape as a guidewire for PCI, and a pressure sensor located near the proximal end of the radiopaque part (~3 cm from the tip) is used to measure the intracoronary pressure. A monorail-type catheter has also been developed for measuring intracoronary pressure and can be used to measure FFR.

The procedure for measurement of FFR is as follows. First, the pressure guidewire is calibrated outside the body. It is then inserted into the guiding catheter and the pressure sensor is aligned with the tip of the guiding catheter, after which the pressure of the pressure sensor is equalized with that of the guiding catheter. Intracoronary administration of a nitrate is performed to prevent coronary spasm due to guidewire insertion, and the diameter of the coronary artery is kept constant between maximal hyperemia and baseline. Next, the pressure guidewire is advanced to the distal end of the coronary artery segment for measurement and a vasodilator (adenosine, ATP, papaverine hydrochloride, nicorandil, etc.) is administered to induce myocardial hyperemia, followed by simultaneous measurement of the distal pressure (Pd) using the pressure guidewire and the proximal pressure (Pa) at the tip of the guiding catheter during myocardial hyperemia to provide data for calculation of FFR. Subsequently, the pressure guidewire may be pulled back slowly while measuring the coronary pressure to determine the distribution of coronary artery lesions and to identify the lesion causing myocardial ischemia (pullback pressure measurement). Finally, the pressure sensor on the pressure guidewire is aligned with the tip of the guiding catheter again to confirm that there has been no pressure drift during measurement.

19.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

19.2.1 Objectives of FFR Measurement

The objectives of measuring FFR are (1) to judge whether coronary artery stenosis is causing myocardial ischemia, (2) to evaluate the extent of reduction in coronary blood flow, (3) to judge the indications for coronary revascularization and select appropriate treatment, (4) to predict the prognosis, and (5) to assess the improvement of coronary flow after revascularization.
19.2.2 Indications
Measurement of FFR is indicated in patients with coronary artery stenosis who have not undergone assessment of ischemia using other methods for diagnosing myocardial ischemia, or in whom assessment of ischemia has been performed by other methods but the diagnosis of myocardial ischemia remains unclear. In general, lesions causing moderate stenosis (30–70% stenosis) on coronary angiography are the best indication. However, FFR may be positive in a stenosis that appears to be mild on angiography or negative in an angiographically severe stenosis. Therefore, if the diagnosis of myocardial ischemia is unclear in patients with mild or severe stenosis, FFR may be measured, if it can be done safely. In patients with serial lesions and diffuse lesions, coronary plaques present in the same vessel may collectively cause significant impairment of blood flow even if individual stenoses look mild on coronary angiography. Therefore, these lesions also represent a good indication for FFR measurement.

Multivessel disease is another good indication for measurement of FFR. In patients with multivessel disease, it is often difficult to accurately assess the presence and extent of myocardial ischemia by coronary angiography or noninvasive diagnostic methods. FFR allows accurate assessment of blood flow on the basis of each coronary artery, even in the presence of multivessel disease. In studies where FFR was measured in patients who were judged to have multivessel disease on coronary angiography, the number of diseased vessels was changed and the treatment plan was modified in many patients. In addition, outcomes were better when treatment was modified according to the FFR findings than when treatment was selected without taking account of the FFR results.

Left main coronary artery disease is another setting in which accurate assessment of myocardial ischemia is difficult using coronary angiography or noninvasive diagnostic methods, and this is accordingly a good indication for FFR measurement. It is reported that prognosis was good when coronary revascularization was performed based on positive results of FFR measurement and also when revascularization was deferred in the case of negative FFR. For evaluation of left main coronary artery disease, the pressure guidewire should be inserted into the left anterior descending artery or left circumflex artery and is better to be placed into the coronary artery (left anterior descending or left circumflex) with little or no stenosis. It needs to be borne in mind that FFR values can be affected even when the pressure wire is positioned in a nondiseased vessel in the presence of hemodynamically severe stenosis in the vessel opposite to that in which the pressure wire is placed. In such a case, care should be exercised when interpreting the findings.

It has been reported that stenotic lesions in bypass grafts can be assessed by FFR, but it should be noted that evidence is limited compared with that for native coronary lesions.

FFR can be measured to assess the effect of coronary revascularization (i.e., the extent of improvement in myocardial blood flow after revascularization). In particular, the FFR values measured after balloon dilatation of lesions and after stent implantation have been reported to be associated with subsequent clinical outcomes.

19.2.3 Contraindications
FFR cannot be measured when administration of vasodilators to induce myocardial hyperemia is contraindicated, such as in patients with drug allergies or asthma in the case of adenosine. Even when use of adenosine is contraindicated, availability of other agents may allow FFR measurement to be performed. In lesions with total occlusion, FFR measurement is impossible because the distal pressure cannot be measured by the pressure guidewire.

In patients with ST-elevation myocardial infarction, it is considered that achieving maximal hyperemia in the infarct-related vessel is impossible because of the microcirculatory dysfunction and accordingly the measurement of FFR is not recommended. However, the measurement of FFR in nonculprit lesions (those not responsible for myocardial infarction) has been reported to be unaffected by infarction, and can be performed during the same PCI procedure for the culprit lesion in patients with ST-elevation myocardial infarction. Treatment of nonculprit lesions that cause significant ischemia according to the FFR values has been reported to be effective on a cost–benefit basis. The measurement of FFR is not recommended in extremely tortuous or extensively calcified lesions because insertion of the pressure guidewire is considered to be dangerous or impossible or the FFR values might not be reliable due to the accordion phenomenon.

19.2.4 Diagnostic Performance for Myocardial Ischemia
A study that assessed the accuracy of FFR for diagnosing myocardial ischemia (using FFR <0.75 as the criterion for significant ischemia) in comparison with exercise ECG, dobutamine stress echocardiography, and stress myocardial scintigraphy showed a sensitivity of 88%, specificity of 100%, positive predictive value of 100%, negative predictive value of 88%, and diagnostic accuracy of 93%. In subsequent studies, the diagnostic accuracy of FFR was also found to be 75–97%. Thus, FFR is currently considered to be the method with the highest accuracy for diagnosing myocardial ischemia caused by epicardial coronary artery stenosis.

19.2.5 FFR and Clinical Outcomes
It has been reported that better clinical outcomes can be obtained when coronary revascularization is performed on the basis of FFR measurement rather than angiographic findings. Hence, if revascularization is scheduled for coronary lesions and myocardial ischemia has not been demonstrated by another method of functional assessment, FFR should be performed.

When FFR is ≤0.80, addition of revascularization to medical treatment has been reported to improve subsequent clinical outcomes compared with medical treatment alone, with the improvement of clinical outcomes being mainly due to a decrease in future emergency revascularization. Accordingly, coronary revascularization should be considered when FFR is ≤0.80. Conversely, it has been reported that the prognosis is favorable when FFR is >0.80, even if revascularization is not performed, suggesting that coronary revascularization is not required for lesions with FFR >0.80. However, correction of coronary risk factors should be actively implemented after revascularization is differed based on negative FFR.

19.2.6 Interpretation of FFR Values
a. Cutoff Value of FFR for Myocardial Ischemia
The cutoff value of FFR for myocardial ischemia is <0.75. This value was determined by comparison with multiple
noninvasive diagnostic methods for ischemia. Follow-up studies have provided support for a cutoff value of 0.75–0.80, with an FFR of 0.75–0.80 being considered the gray zone for myocardial ischemia.\textsuperscript{729,730} FFR is an index of the severity of blood flow impairment caused by epicardial coronary artery stenosis. Although FFR ≤0.75 is likely to be associated with myocardial ischemia, FFR ≥0.75 can also be associated with ischemia in the presence of microvascular disease.

b. Cutoff Value of FFR for Revascularization

The cutoff value of FFR when deciding the indication for coronary revascularization is ≤0.80, because clinical outcomes improved when FFR ≤0.80 was used as the cutoff value for revascularization in large-scale clinical studies.\textsuperscript{314,315,732} A meta-analysis and a large prospective registry study have also supported a cutoff value of 0.75–0.80 for improvement of clinical outcomes by coronary revascularization.\textsuperscript{735,736} On the other hand, for FFR ≥0.75, the prognosis was reported to be favorable even if revascularization of lesions was deferred.\textsuperscript{733,734} Therefore, FFR of 0.75–0.80 is considered to be the gray zone for revascularization.

c. Interpretation of FFR as a Continuous Variable

Although FFR ≤0.80 is used as the cutoff value when deciding the indication for revascularization, FFR is actually a continuous variable that ranges from 0 to 1.0. When FFR is ≤0.80, impairment of blood flow due to epicardial coronary artery stenosis is more severe as FFR values become lower. Conversely, when the FFR is >0.80, higher FFR values mean less impairment of blood flow. Therefore, the effectiveness of coronary revascularization and medical therapy, as well as subsequent clinical outcomes, will vary depending on the FFR value. In particular, there is a negative correlation between the FFR value and the incidence of cardiovascular events when revascularization is deferred.\textsuperscript{735,737}

19.2.7 Determining the Indication for Coronary Revascularization

a. Indication for Revascularization

Coronary revascularization is indicated for lesions when the FFR is ≤0.80, based on reports that the addition of revascularization to medical therapy leads to better clinical outcomes than drug therapy alone when the FFR of a lesion is ≤0.80.\textsuperscript{314,732} However, this should not be interpreted as meaning that revascularization is required for all lesions with FFR ≤0.80. If the FFR is ≤0.80, but the lesion is diffuse or there is small vessel disease where revascularization is not likely to be effective or the lesion is so complex that revascularization cannot be performed safely, medical therapy instead of revascularization might be an appropriate clinical decision. Performing revascularization can generally be justified if FFR is ≤0.80 at the time of the procedure.

b. Avoiding Revascularization

Revascularization should generally be avoided when the FFR is >0.80, because it has been reported that clinical outcomes can be worse after revascularization of such lesions compared with medical therapy.\textsuperscript{314,732,735}

c. Approach to Lesions With a “Gray Zone” FFR

Studies have found different results when the FFR is in the range of 0.75–0.80, and there is no consensus on the treatment strategy.\textsuperscript{738,739} Therefore, treatment should be decided by comprehensive consideration of patient and lesion characteristics in addition to the FFR value.

d. Selection of the Revascularization Method (PCI or CABG)

There is considerable evidence regarding the use of FFR together with PCI, but only limited evidence is available for CABG. In previous reports, FFR ≤0.80 was used as the cutoff value when deciding the indication for CABG. This is the same cutoff value as for PCI, suggesting that it may be reasonably used for CABG.\textsuperscript{740,741} It should be noted, however, that there has not been adequate verification of whether this is the optimal cutoff value for CABG.

19.2.8 Evaluation After Coronary Revascularization

Measurement of the FFR after revascularization allows the effectiveness of treatment to be assessed. For example, improvement of the FFR of a lesion from 0.60 to 0.90 after treatment means that revascularization has improved coronary blood flow by 30 percentage points and has probably alleviated myocardial ischemia.\textsuperscript{727} In addition, the FFR values measured after catheter procedures have been reported to be associated with subsequent clinical outcomes and can thus be used as the endpoint for catheter treatment.

A good clinical outcome had been reported at 2 years after balloon angioplasty when the postprocedural FFR value is ≥0.90,\textsuperscript{735} and a low incidence of events has been reported at 6 months after bare metal stent implantation when the FFR is ≥0.90.\textsuperscript{727} In addition, the clinical outcome is better after DES implantation when the FFR is ≥0.89–0.92 than with lower FFR values.\textsuperscript{727,742,743} Although there were some differences in the endpoint values among the studies, higher FFR values were associated with lower clinical event rates. However, it is often difficult to achieve high postprocedural FFR values in patients with diffuse or long lesions. Attempts to achieve a high FFR value may lead to an increase in the total stent length and number of stents, as well as increasing the risk of complications and medical costs. Thus, it should be noted that although higher FFR values after PCI are associated with better clinical outcomes, the association between making extensive efforts to improve the FFR value and better clinical outcomes remains to be verified.\textsuperscript{744}

19.2.9 Economic Benefits of FFR-Based Coronary Revascularization

It has been reported that FFR-guided PCI not only improves clinical outcomes compared with angiography-guided PCI, but also achieves better medical economy,\textsuperscript{572} primarily because medical costs are reduced by avoiding unnecessary coronary revascularization.

It has also been reported that for lesions with significantly reduced FFR, the initial cost of revascularization is higher than that of medical therapy alone, but the cost eventually becomes similar. This is because avoiding coronary revascularization for lesions with significantly reduced FFR results in a later increase in the revascularization rate, leading to escalation of medical costs. Given that clinical outcomes are better compared with medical therapy alone and long-term medical costs are equivalent, performing revascularization of lesions with significantly reduced FFR seems to represent an effective use of medical resources.\textsuperscript{745}
19.2.10 Instantaneous Wave-Free Ratio (iFR)

Similar to FFR, iFR is another parameter of functional coronary stenosis that is based on coronary artery pressure obtained by a pressure guidewire. \(^{746}\) iFR is also calculated as the ratio of the pressure distal to the stenosis (Pd) to the pressure proximal to the stenosis (Pa). However, FFR is measured during drug-induced maximal myocardial hyperemia, whereas iFR is measured under resting conditions. Also, the FFR is the mean Pd/Pa ratio over the entire cardiac cycle, whereas iFR is measured during the last 75% of diastole, which is called the wave-free period. Accordingly, iFR is calculated as Pd/wave-free period/Pa/wave-free period, and coronary artery stenosis is judged to be hemodynamically significant when iFR is ≤0.89. \(^{747}\) The same cutoff value (iFR ≤0.89) is used for diagnosis of myocardial ischemia and as the indication for coronary revascularization. \(^{748,749}\)

The diagnostic accuracy of iFR vs. FFR has been tested but further assessment is required to determine their clinical usefulness. \(^{750}\) Recommendations and levels of evidence for this procedure are shown in Table 43.

### Table 43. Recommendations and Levels of Evidence for Invasive Intracoronary Pressure Measurements for the Diagnosis of Chronic Coronary Heart Disease

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR/iFR are recommended for assessing hemodynamic significance of epicardial coronary artery stenosis</td>
<td>I</td>
<td>A</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>FFR/iFR are recommended for decision-making on PCI indication</td>
<td>I</td>
<td>A</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>FFR/iFR are considered for decision-making on CABG indication</td>
<td>Iib</td>
<td>B</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>FFR might be useful for assessing post-PCI results</td>
<td>Iib</td>
<td>C</td>
<td>B</td>
<td>IVa</td>
</tr>
</tbody>
</table>

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

### 20. Measurement of Coronary Flow Velocity

#### 20.1 Characteristics and Technical Aspects

Measurement of coronary blood flow velocity is generally performed in order to obtain the CFVR. The CFR (CFVR) is an index of the increase in coronary flow (velocity) during myocardial stress compared with at rest, and is defined as the ratio of coronary blood flow (velocity) during stress to coronary blood flow (velocity) at rest. \(^{760,761}\) PET can be used to quantitatively assess myocardial blood flow and calculate the CFR. \(^{760,761}\) However, CFVR is more often calculated from coronary blood flow velocity data obtained with echocardiography or a Doppler guidewire. \(^{748,749}\) To calculate the CFVR based on the coronary blood flow velocity, it is assumed that the vessel diameter is the same at rest and under stress, which means the ratio of coronary blood flow velocity during stress to that at rest is the same as the coronary blood flow ratio. Therefore, the CFVR (the ratio of coronary blood flow velocity) is calculated to obtain CFR.

In the past, catheter-based Doppler blood flow measurement was done in some cases, \(^{763}\) but the CFVR is now measured during cardiac catheterization by either a guidewire with a Doppler sensor or a dual guidewire equipped with both a Doppler sensor and a pressure transducer. \(^{764,765}\) When the CFVR is measured with a guidewire, intracoronary nitrate is administered before the wire is inserted into the coronary artery to prevent coronary spasm and achieve maximal vasodilation. To assess the influence of coronary stenosis on the CFVR, the wire should be positioned such that the Doppler sensor is located at a distance of 5–10 vessel diameters (≥20 mm) from the stenosis. It should also be noted that the sample volume is located 5 mm distal to the sensor of the wire. In 10–15% of patients, it is difficult to obtain a clear blood flow signal. In such cases, the wire should be manipulated to adjust the position and direction of the Doppler sensor in order to obtain a blood flow signal of the highest quality possible. \(^{750}\)

CFVR can be calculated as the ratio of the average peak velocity (APV) with myocardial hyperemia to that at rest (APV hyperemia/APV rest). Maximal myocardial hyperemia is induced by continuous intravenous infusion or intracoronary administration of adenosine or ATP, intracoronary administration of papaverine hydrochloride, or intracoronary administration of nicorandil, etc. The CFVR can also be determined during cardiac catheterization by the thermodilution method using a temperature sensor attached to a pressure guidewire. With this method, a pressure guidewire is inserted into the target coronary artery and bolus intracoronary administration of saline at room temperature is performed through the guiding catheter, followed by measurement of the mean transit time (Tmn). Coronary flow velocity can be estimated by the inverse Tmn, and then the CFVR is calculated as the ratio of inverse Tmn during maximal myocardial hyperemia to Tmn at rest. \(^{766,767}\)

Transthoracic or transesophageal echocardiography can be performed for noninvasive visualization of coronary flow velocity signals by color Doppler imaging. The sample volume is set above the coronary flow velocity signals using a pulsed Doppler method so that temporal changes in coronary flow velocity signals can be recorded, allowing the CFVR to be calculated from the mean flow velocity measured at rest and that measured during maximal hyperemia. \(^{762}\)
20.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

20.2.1 Objectives of Measuring CFR and CFVR

CFR and CFVR are indices that reflect myocardial ischemia caused by epicardial coronary artery lesions and coronary microvascular dysfunction. As such, these indices are used to determine the severity of hemodynamic stenosis caused by coronary lesions and to assess coronary microvascular dysfunction. Because it is impossible to separate the contribution of epicardial coronary artery lesions and microvascular dysfunction to myocardial ischemia by CFR, care should be exercised when interpreting the results when deciding the indications and effectiveness of PCI.

20.2.2 Indications

Coronary flow velocity can be measured to assess the hemodynamic severity of coronary stenosis, and can also be used to assess the severity of coronary microvascular dysfunction.

20.2.3 Contraindications

Measurement of CFR or CFVR is impossible when administration of vasodilators to induce maximal myocardial hyperemia is contraindicated, such as in patients with drug allergies or asthma in the case of adenosine. Even when adenosine is contraindicated, other agents may be available that allow measurement of CFR or CFVR. Insertion of a guidewire should be avoided for lesions where this is considered to be dangerous or impossible, such as tortuous or heavily calcified lesions. In patients with total occlusion, the retrograde or anterograde collateral flow velocity can be detected distal to the occlusion if insertion of a Doppler guidewire with a microcatheter is successful after crossing the lesion with the guidewire, allowing CFR or CFVR to be calculated.

20.2.4 Diagnostic Performance

The diagnostic performance of CFR or CFVR for myocardial ischemia using a cutoff value <2.0 has been reported to be as follows: sensitivity of 86–92%, specificity of 89–100%, diagnostic accuracy of 89–96%, positive predictive value of 84–100%, and negative predictive value of 77–95%.

20.2.5 Interpretation of Measured Values

In general, myocardial ischemia is judged to be present when CFR or CFVR is <2.0 but the normal value varies among reports. In animals and healthy adults, the CFR or CFVR is reported to be in the range of 3.5–5. In patients with coronary risk factors but without coronary stenosis, the CFR has been reported to be 2.6–2.7.

Hemodynamically significant epicardial coronary artery lesions and coronary microvascular dysfunction can be ruled out if the CFR or CFVR is ≥2.0 and myocardial ischemia is negative. If the CFR or CFVR is <2.0 and myocardial ischemia is positive, myocardial ischemia is considered to be due to epicardial coronary artery lesions or microvascular obstruction, or both causes. Even if myocardial ischemia is positive with the CFR or CFVR, epicardial coronary artery lesions cannot be identified as the cause; hence, these are not suitable indices for deciding the indications for revascularization.

It should also be noted that CFR (and CFVR) are calculated from the ratio of blood flow (velocity) at maximal myocardial hyperemia to blood flow (velocity), at rest and thus are affected by factors that can alter both resting and hyperemic blood flow (velocity). Thus, these parameters are influenced by hemodynamic changes (heart rate and blood pressure), preload and afterload of the left ventricle, left ventricular systolic function, cardiac mass, etc.

20.2.6 Relationship to Clinical Outcomes

Several studies have found an association between CFR or CFVR and prognosis. The number of cardiovascular events is increased when CFR or CFVR is <2.0 compared with when these parameters are ≥2.0. Regarding the indications for coronary revascularization, it has been shown that deferral of revascularization in intermediate stenoses is safe when the CFR or CFVR is ≥2.0. In terms of postrevascularization assessment, it has been shown that patients with both ≤35% residual stenosis and a CFR or CFVR ≥2.5 following balloon angioplasty have subsequent favorable outcomes.

20.2.7 Combined Coronary Flow Velocity and Intracoronary Pressure Measurement

CFR or CFVR does not allow separate assessment of the effect of epicardial coronary artery lesions and coronary microvascular dysfunction. However, it has been proposed that adding intracoronary pressure information to coronary flow velocity data may help to separate the influence of coronary artery lesions from that of coronary microvascular dysfunction. Simultaneous measurement of coronary flow velocity and intracoronary pressure is possible by using a dual sensor guidewire.

a. Baseline Stenosis Resistance (BSR) Index

The BSR index is a measure of the vascular resistance caused by coronary stenosis at rest, and it is specific for epicardial coronary artery stenosis. It is calculated as: baseline Pa – baseline Pd/baseline APV.

b. Hyperemic Stenosis Resistance (HSR) Index

The HSR index measures the vascular resistance caused by coronary stenosis at maximal myocardial hyperemia, and it is also specific for epicardial coronary artery stenosis. It is calculated as: hyperemic Pa – hyperemic Pd/hyperemic APV.

c. Microvascular Resistance (MVR)

MVR specifically assesses the vascular resistance of the coronary microcirculation. MVR at rest is calculated as: baseline Pd/baseline APV, and MVR at maximal myocardial hyperemia is calculated as: hyperemic Pd/hyperemic APV.

d. Index of Microcirculatory Resistance (IMR)

The IMR specifically assesses the vascular resistance of the coronary microcirculation, which is determined by using a pressure guidewire with the thermodilution method. IMR is calculated as the product of mean hyperemic Pd and hyperemic Tmn.

e. Lack of Agreement Between FFR and CFR or CFVR

By measuring both FFR and CF(V)R in the same coronary artery, more detailed assessment of coronary pathophysiology is possible. If both FFR and CF(V)R are negative for ischemia in the same coronary artery, it can be
concluded that coronary blood flow is adequate and neither coronary artery lesions nor dysfunction of the coronary microcirculation is causing myocardial ischemia. On the other hand, if FFR and CF(V)R are both positive for ischemia, there is likely to be significant hemodynamic stenosis in the target coronary artery. However, discordant results for FFR and CF(V)R have been reported in about 30–40% of lesions. When CF(V)R is positive for ischemia and FFR is negative, this may indicate the presence of coronary microvascular dysfunction. On the other hand, if CF(V)R is negative for ischemia and FFR is positive, the coronary microcirculation should be adequate and it can also be suggested that coronary artery lesions are not causing significant stenosis. In this setting, the decrease in FFR may result from an increase in the pressure gradient due to a marked increase in coronary blood flow (velocity) at maximal myocardial hyperemia, although coronary stenosis is not so severe. This may also represent a state in which coronary blood flow (velocity) is maintained while coronary artery pressure decreases. Recommendations and levels of evidence for this procedure are shown in Table 44.

<table>
<thead>
<tr>
<th>Measurements</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
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<tr>
<td>CF(V)R can be used to assess the degree of myocardial ischemia as the</td>
<td>Ila</td>
<td>B</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>combination of epicardial coronary artery stenosis and microvascular disease</td>
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<td>BSR/HSR might be considered for the assessment of epicardial coronary</td>
<td>Iib</td>
<td>C</td>
<td>B</td>
<td>IVb</td>
</tr>
<tr>
<td>artery stenosis</td>
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<tr>
<td>IMR/MVR might be considered for the assessment of microvascular disease</td>
<td>Iib</td>
<td>C</td>
<td>B</td>
<td>IVa</td>
</tr>
</tbody>
</table>

Table 44. Recommendations and Levels of Evidence for Invasive Intracoronary Coronary Flow Velocity Measurements

II. Risk Assessment and Management

1. Comprehensive Risk Management

Patients with coronary heart disease have a higher risk of recurrent cardiovascular events than persons receiving primary prevention, and various interventions are important for these patients, including lifestyle modification, exercise, diet, and drug therapy. Risk factors for coronary heart disease include hypertension, diabetes mellitus, dyslipidemia, CKD, and smoking. Recent large-scale clinical studies have demonstrated the usefulness of aggressive antihypertensive therapy for patients with hypertension. However, there is little Japanese evidence regarding the value of strict antihypertensive therapy in hypertensive patients with coronary heart disease, and the current goal of treatment is a blood pressure <140/90 mmHg.

In patients with multiple risk factors, such as prior myocardial infarction, diabetes mellitus, CKD, dyslipidemia, smoking, and a positive family history, the target blood pressure is set at <130/80 mmHg after confirming the absence of significant coronary artery stenosis and myocardial ischemia or changes on ECG. In patients with concomitant diabetes mellitus, the age, duration of diabetes mellitus, complications, and risk of hypoglycemia must be considered. According to the 2016 Japan Diabetes Society Clinical Practice Guideline, the target HbA1c is ≤7.0% for prevention of complications.

Management of dyslipidemia with aggressive lipid-lowering therapy, primarily statins, has been well documented in patients requiring secondary prevention. The 2017 Guidelines for Prevention of Atherosclerotic Cardiovascular Disease set a target of <100 mg/dL for LDL-cholesterol in patients who require secondary prevention. For patients who have FH, ACS, or high-risk diabetes mellitus and a high risk of recurrent events despite secondary prevention, stricter lipid-lowering therapy is recommended, with LDL-cholesterol <70 mg/dL being the target, as in Western guidelines. Patients receiving secondary prevention often have these comorbidities, so comprehensive management is essential.

Prevention of cardiovascular events in patients with coronary heart disease is important both clinically and in terms of medical economics, because these events are more frequent in such patients than in the general population. Comprehensive risk management is clearly important because epidemiological studies have shown that hypertension, diabetes mellitus, dyslipidemia, smoking, and CKD are risk factors for arteriosclerosis and development of cardiovascular events, and many patients have multiple risk factors, increasing the risk of events occurring. Observational studies performed in Western countries have shown that better management of multiple risk factors improves the long-term prognosis of patients with coronary heart disease.

In Japan, the J-DOIT3 study (published in 2017) demonstrated the usefulness of aggressive long-term intervention for control of glucose, blood pressure, lipids, and obesity, although the study population consisted of patients with diabetes mellitus receiving primary prevention.

Aggressive intervention, including lifestyle modification/exercise, dietary therapy, and drug therapy, is important for preventing recurrent cardiovascular events.

1.1 Hypertension

Hypertension is a major risk factor for coronary heart disease and cerebrovascular disease, and is also the most common coronary risk factor encountered in daily clinical practice. According to NIPPON DATA 2010, 43 million
persons were estimated to have hypertension in Japan in 2010. An association between hypertension and development of cardiovascular disease has been clarified by both domestic and foreign cohort studies. EPOCH-JAPAN, a meta-analysis of major cohort studies performed in Japan, showed that the risk of death from cardiovascular disease increases as the blood pressure rises above the optimal level (systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg). On the other hand, large-scale clinical studies performed in Western countries in the 1990s consistently set a higher target for the blood pressure and found no further decrease in events if it was reduced below 140/90 mmHg. According to the current ACC/AHA guidelines for management of hypertension set the target blood pressure <130/80 mmHg in patients with multiple risk factors, such as a history of myocardial infarction, diabetes mellitus, CKD, dyslipidemia, smoking, and positive family history, as well as a history of myocardial infarction, diabetes mellitus, CKD, dyslipidemia, smoking, and positive family history, as well as a history of myocardial infarction, diabetes mellitus, CKD, dyslipidemia, smoking, and positive family history.

Interestingly, the SPRINT study demonstrated the usefulness of strict blood pressure control, in contrast to the fact that there has been no change in the target blood pressure recommendations over the past 20 years. The study showed that aggressive antihypertensive therapy targeting a systolic blood pressure <120 mmHg was associated with a significant reduction in the composite endpoint of ACS, stroke, decompensated heart failure, and cardiovascular death, as well as a reduction in all-cause death, compared with standard therapy (target blood pressure <140 mmHg) in patients at high risk of cardiovascular disease. However, it should be noted that the SPRINT trial excluded patients with a history of diabetes mellitus, CKD, or stroke, which represent important subpopulations of the patients receiving secondary prevention in real-world clinical settings. A meta-analysis of 42 studies (144,220 patients) also showed a significant reduction in the incidence of cardiovascular events when the systolic blood pressure was maintained at 120–124 mmHg, which is lower than the conventional target blood pressure. Based on such new evidence, the current ACC/AHA guidelines for management of hypertension set the target at <130/80 mmHg in hypertensive patients with chronic coronary heart disease. On the other hand, there is little evidence about the efficacy of aggressive antihypertensive therapy for hypertensive Japanese patients with coronary heart disease. At present, 140/90 mmHg should still be the target for secondary prevention, as recommended by the Japanese Society of Hypertension, and 130/80 mmHg should be the target for patients with the abovementioned conditions.

### 1.2 Diabetes Mellitus

Previous epidemiological studies have shown that diabetes mellitus (DM) increases the risk of stroke and cardiovascular disease by about 2- to 4-fold. A meta-analysis also demonstrated that a 1% increase in HbA1c was associated with an 18% increase in cardiovascular events. In addition, it has been reported that patients with cardiovascular disease secondary to DM have higher rates of cardiovascular mortality and recurrent events. Based on the results of observational studies, which showed that an increase in events is associated with elevation of blood glucose, it was speculated that development of macroangiopathy could be suppressed by reducing the blood glucose level. Subsequently, intervention studies using strict glycemic control were conducted, including ACCORD, ADVANCE, and VADT, but these studies revealed that several years of intensive management did not reduce the incidence of macroangiopathy. In fact, the ACCORD study found a significant increase in mortality in the intensive treatment group. The study indicates that this outcome occurred because strict glycemic control increases the frequency of hypoglycemia. In contrast, early glycemic control has been reported to reduce long-term complications and mortality (legacy effect), and early glycemic control, while avoiding hypoglycemia is considered to be important.

The glycemic control target must consider the patient’s age, duration of DM, comorbidities, and risk of hypoglycemia among other factors. In the 2016 Japanese Diabetes Society Clinical Practice Guideline published by the Japan Diabetes Society, the target HbA1c is set at ≤7.0% from the viewpoint of preventing complications. Metformin is recommended as a globally accepted first-line antidiabetic drug. Use of SGLT2 inhibitors and GLP-1 receptor agonists, which were found to reduce cardiovascular events in large-scale clinical studies reported in 2017, has also been recommended, but it remains unclear which patients should be treated with these drugs. Whichever medication is used, more attention must be paid to hypoglycemia, adverse reactions, and potential effects on the cardiovascular system.

Comprehensive management, including control of blood pressure and lipid-lowering therapy with statins, is essential because patients with DM have a high incidence of cardiovascular events. The 2017 Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases state that patients who have DM associated with noncardiogenic cerebral infarction, PAD, CKD, metabolic syndrome, or smoking are a high-risk population for secondary prevention, in addition to patients with FH and ACS, and recommend aggressive lipid-lowering therapy with LDL-cholesterol <70 mg/dL as the target.

### 1.3 Dyslipidemia

Dyslipidemia is a generic term that refers to elevation of total cholesterol, LDL-cholesterol (LDL-C), and/or triglycerides, or a low level of HDL-cholesterol. The greatest amount of evidence, including intervention studies, has been...
A combination of statins and ezetimibe leads to plaque regression. Recent studies have also demonstrated that adding other cholesterol-lowering drugs, such as ezetimibe and PCSK9 inhibitors, to statin therapy can further reduce cardiovascular events. Based on the results of these clinical studies, the following statement was added to the 2017 ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation: consider combining PCSK9 inhibitors or ezetimibe if LDL-cholesterol does not reach the target level of <70 mg/dL even with use of the maximum tolerable dose of a statin.

In Japan, the LDL-C target for patients with a history of coronary heart disease receiving secondary prevention is <100 mg/dL. In the 2017 revision of the Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases, it also states that patients receiving secondary prevention should be managed with a target LDL-C level <100 mg/dL, and if this is difficult to achieve, reduction of LDL-C by at least 50% should be attempted (Table 45). However, more stringent lipid-lowering therapy is recommended for high-risk patients, such as those with FH, ACS, and high-risk diabetes mellitus, with an LDL-C level <70 mg/dL as the target, corresponding to the guidelines from Western countries (Figure 18).

The high doses of statins recommended in Western guidelines are not covered by health insurance in Japan, which only funds moderate statin doses, partly because there have been few Japanese interventional studies of

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**Table 45. Lipid Management Targets for Patients With Different Risk Category**

<table>
<thead>
<tr>
<th>Therapeutic principle</th>
<th>Management category</th>
<th>Lipid management target (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL-C</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>Low risk</td>
<td>&lt;160</td>
</tr>
<tr>
<td>Drug therapy should be</td>
<td>Moderate risk</td>
<td>&lt;140</td>
</tr>
<tr>
<td>considered after lifestyle</td>
<td>High risk</td>
<td>&lt;120</td>
</tr>
<tr>
<td>modification</td>
<td>History of CAD</td>
<td>&lt;100 (&lt;70)*</td>
</tr>
</tbody>
</table>

* For patients who are also suffering from high-risk conditions, such as FH, ACS, and diabetes complicated by other high-risk conditions shown in SubTable b, stricter LDL-C control should be considered, with a level of <70 mg/dL as the target.

• Although non-drug therapy is used as a standard means for achieving the management target in primary prevention, drug therapy should be considered for patients with low risk if the LDL-C level is ≥180 mg/dL. The possibility of FH should also be considered (see Chapter 5 of the source document).

• Achieving the LDL-C management target should be the first goal, and reaching the non-HDL-C management target should be the next goal after the first goal has been achieved. Managing the TG and HDL-C levels is important during this process.

• These values are challenging goals by utmost effort; a 20–30% reduction in LDL-C levels for primary prevention (low or moderate risk) and a decrease of ≥50% for secondary prevention are also possible targets.

• For elderly patients (aged ≥75 years), refer to Chapter 7 of the source document.

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**SubTable: Patient Conditions That Require Stricter Management in Secondary Prevention**

| a Familial hypercholesterolemia (FH) |
| Acute coronary syndrome (ACS) |
| Diabetes mellitus (DM) |
| b Noncardiogenic cerebral infarction |
| Peripheral artery disease (PAD) |
| Chronic kidney disease (CKD) |
| Metabolic syndrome |
| Overlap of major risk factors |
| Smoking |

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides. (Reproduced from Kinoshita et al 2018, with permission.)
lipid-lowering therapy for secondary prevention with cardiovascular events such as cardiovascular death as the endpoint, as mentioned above. Under these circumstances, the results of the REAL-CAD study were published in 2017. This study enrolled 14,774 patients aged 20–80 years with stable angina from 733 institutions nationwide, with the patients being randomly allocated to receive 1 mg or 4 mg of pitavastatin daily. Significant reduction of cardiovascular events (19%) was found in the 4-mg group. Notably, there was significant reduction of events such as all-cause death, myocardial infarction, and repeat revascularization, with similar results being obtained after stratification for age, sex, or other variables. In view of these findings, it is recommended that patients with stable angina should receive statin therapy at the highest possible dose within the scope of health insurance coverage.819

An increase in triglycerides, both fasting and nonfasting, is known to predict future coronary heart disease and stroke, as well as death, and monitoring triglycerides is an important part of risk management during statin therapy. The EMPATHY study performed in Japan demonstrated that elevation of triglyceride levels was associated with new-onset coronary heart disease in high-risk patients with diabetes mellitus receiving statins who had retinopathy and hypercholesterolemia.820

1.4 CKD

CKD is an important risk factor for arteriosclerosis. A large-scale registry study previously showed that the risk of all-cause death and cardiovascular disease increased as the eGFR declined in patients with an eGFR <60 mL/min/1.73 m².821 The mortality rate of dialysis patients was 40-fold higher than that of controls without kidney disease, and it should be noted that over 50% of deaths were from cardiovascular disease.822

CKD patients often have hypertension and diabetes mellitus as the underlying diseases, making it important to screen for arteriosclerotic diseases in this patient population. Comprehensive risk management is also necessary. Although large-scale clinical studies have not demonstrated that statins are effective for secondary prevention in dialysis patients,823,824 the efficacy of statins has been verified in CKD patients who were not on dialysis.825,826 Therefore, statin therapy is recommended from the early stage of CKD. For management of blood pressure, antihypertensive therapy with an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker is recommended, especially in patients with proteinuria, because an organ protective effect can be expected with such treatment.827,828

1.5 Smoking

Cigarette smoking is an independent risk factor for cardiovascular disease, and it is clear that smoking promotes arteriosclerosis.829,830 The incidence of coronary heart disease caused by smoking is known to increase in proportion to the extent and duration of smoking. Even at low levels, cigarette smoking is associated with a higher cardiovascular risk.831 So cessation of smoking is strongly recommended for patients receiving secondary prevention or at high risk of cardiovascular disease. It is also a social responsibility to avoid passive exposure to cigarette smoke in homes, public facilities, and workplaces, because passive smoking is also associated with an increase in cardiovascular events.832

Observational studies have demonstrated that cessation of smoking significantly reduces the risk of cardiovascular events. In a Japanese observational study of patients with acute myocardial infarction, nonsmokers had a 61% lower risk of all-cause death than smokers.833 According to a meta-analysis of patients with coronary heart disease, cessation of smoking reduced the relative risk of death by 36%.834 Although these studies indicating an impact of smoking cessation were all observational, it should be recognized that cessation of smoking is no less effective than drug therapy for other risk factors. However, it is not uncommon to find that patients cannot quit smoking and continue to smoke because of nicotine dependence, even if guidance on quitting is provided. In such cases, use of drug therapy to assist smoking cessation should be considered, in addition to counseling. Currently, 12 weeks of treatment for smoking cessation is covered by health insurance in Japan, provided that the medical institution and patient...
meet certain conditions. Thus, treatment should be provided for a certain period together with ongoing guidance about cessation of smoking. Recommendations and levels of evidence for comprehensive risk management are shown in Table 46.

2. Additional Risk Factors and Biomarkers

2.1 Additional Risk Factors and Their Management

2.1.1 Family History

Although the importance of a patient’s family history has been recognized, few large-scale studies have examined the influence on coronary heart disease. Previous cross-sectional studies have shown that a family history of myocardial infarction is associated with an odds ratio of 2 for development of myocardial infarction, and that the risk increases synergistically with the presence of other risk factors such as hypertension and dyslipidemia. Family history was also reported to be an independent risk factor for acute myocardial infarction in Japanese patients with acute myocardial infarction (odds ratio: 1.84, 95% CI: 1.30–2.62, P<0.01). Furthermore, longitudinal studies have identified the family history as a significant risk factor for development of myocardial infarction, with a stronger influence in younger populations. Even if other risk factors are negligible, a positive family history of cardiovascular disease has been shown to influence the occurrence of cardiovascular disease. Therefore, it is important to consider the possibility of OSA and make an appropriate urate-lowering therapy to reduce the incidence of gout and kidney dysfunction associated with hyperuricemia, there is limited evidence from interventional studies about whether such therapy can reduce cardiovascular events, so further investigation is warranted.

2.1.3 Obstructive Sleep Apnea

Although the prevalence of obstructive sleep apnea (OSA) is high among patients with cardiovascular disease, it is often underdiagnosed. Therefore, it is important to consider the possibility of OSA and make an appropriate diagnosis. In patients with coronary heart disease, OSA is strongly associated with major cardiovascular events and increased mortality. In patients with OSA and a history of coronary heart disease or multiple risk factors, CPAP therapy has been reported to reduce the mean 24-hour blood pressure, including the nighttime blood pressure. Secondary prevention of major cardiovascular events with CPAP therapy has not been well documented; however, it is effective for improving sleep and quality of life. It has also been suggested that good adherence to CPAP therapy may have a secondary prevention effect.

2.1.4 Exercise

Many studies have demonstrated that cardiac rehabilitation, especially exercise therapy, is effective for secondary prevention of coronary heart disease. Moderate aerobic exercise (walking, etc.) for a total of ≥30 min per day on at least 5 days per week is generally recommended. However, the type and intensity of exercise should be determined according to the patient’s level of risk and general condition. The amount of physical activity performed during daily life should also be increased through use of stairs and outdoor activities.

2.1.5 Alcohol

In alcohol drinkers, excessive alcohol consumption should be avoided and intake should not exceed 25 g/day. Drinking in moderation is not a risk factor for coronary heart disease.
2.1.6 Influenza Vaccination

Many cohort studies and RCTs have shown that vaccination against influenza reduces cardiovascular morbidity and mortality in patients receiving secondary cardiovascular prevention. Developing influenza in winter may influence the progression of cardiovascular disease, including heart failure and ischemic stroke. On the other hand, a significant decrease in cardiovascular morbidity was not observed after vaccination in a relatively young cohort. Thus, annual vaccination is recommended for patients with chronic coronary heart disease, particularly elderly patients.

2.1.7 Psychological and Social Factors

In patients with myocardial infarction, health-related QOL does not return to the national standard after discharge from hospital, and depressive symptoms are associated with delayed recovery of physical QOL. It has been reported that the risk of recurrent cardiovascular events within 1 year is significantly higher in patients with depressive symptoms after myocardial infarction. Therefore, attention should be paid to psychological factors (depression, anxiety, insomnia, etc.), and referral to a psychiatrist or psychologist should be considered as required.

Sufficient education should be provided to the patient and family on an ongoing basis regarding the need to modify the lifestyle, take medications as scheduled, and visit hospital regularly. The social background of patients and their families should also be considered with social support being provided as necessary.

2.2 Biomarkers and Genetic Risk Scores

2.2.1 Inflammatory Markers

Inflammatory markers are not specific to the cardiovascular system, but many studies have shown that high levels of inflammatory markers, including high-sensitivity C-reactive protein, are independent predictors of restenosis and cardiovascular events, because inflammatory mechanisms are crucially involved in the development and progression of atherosclerosis and the destabilization and disruption of coronary plaques. Because inflammatory markers have been used as surrogate markers in many interventional studies targeting inflammation, they are considered to be one of the most important biomarkers for predicting coronary heart disease.

2.2.2 Lipid and Myocardial Necrosis Markers

Lipid markers include lipoprotein ratios (LDL-/HDL-cholesterol ratio, etc.), postprandial hyperlipidemia, Lp(a), MDA-LDL, remnant lipoproteins, small-dense LDL, and apoprotein B, all of which have been reported to be associated with arteriosclerotic diseases, including coronary heart disease, and have been utilized clinically. For details, see the 2017 Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases, published by the Japan Atherosclerosis Society.

Creatinine kinase and its MB fraction have conventionally been used as enzymatic markers of myocardial necrosis in clinical practice. However, it has become possible to measure high-sensitivity troponin in recent years, allowing a diagnosis of suspected ACS with a high sensitivity and specificity within a few hours after the onset. Clinically, both high-sensitivity troponin T (hs-TnT) and high-sensitivity troponin I (hs-TnI) are used. In a prospective multicenter study of 2,226 patients with suspected non-ST-elevation myocardial infarction, both markers were found to be highly accurate, although hs-TnT was slightly more useful for predicting mortality at 24 months. Elevation of troponin after PCI suggests myocardial damage associated with the procedure, and it has been reported that an elevated troponin level is associated with both the short-term and long-term prognosis.

In a cohort study of 2,029 patients with stable coronary heart disease undergoing elective PCI, elevation of hs-TnT (≥14 ng/L) was observed in 527 patients (26%) before PCI and was an independent predictor of 1-year mortality (adjusted hazard ratio: 2.08; 95% CI: 1.10–3.92, P=0.024). Although high-sensitivity troponin is a myocardial-specific biomarker and excellent prognostic indicator in patients with coronary heart disease, specific interventions for patients with elevated troponin levels and the usefulness of troponin as an index of the efficacy of therapeutic interventions have not been established.

2.2.3 Age- and Sex-Specific Gene Expression Score (ASGES)

ASGES is a risk assessment score that ranges from 1 to 40 and is based on the expression profile of 23 genes determined in peripheral blood leukocytes. In Western countries, it is increasingly accepted as a test that can be used to quantitatively evaluate the risk of coronary heart disease. This risk score correlates with the accuracy of conventional diagnostic procedures such as coronary angiography and CCTA, with a low score indicating low likelihood of coronary heart disease. An ASGES ≤15 has a sensitivity of 89% for detection of coronary heart disease, together with a specificity of 52% and a negative predictive value of 96%. Patients with scores in this range showed no abnormal findings on subsequent stress tests or coronary angiography, and had a low rate of coronary revascularization or major cardiovascular events during 1-year follow-up (1.2% in the ASGES ≤15 group vs. 4.5% in the ASGES >15 group; P=0.03).

The odds ratio for coronary heart disease in the ASGES >15 group compared with the ASGES ≤15 group was 2.5 (95% CI: 1.6–3.8, P<0.001), and the incidence of a composite endpoint of major cardiovascular events was also higher in the former group (adjusted hazard ratio: 1.70; 95% CI: 1.10–2.64, P=0.017). Thus, ASGES is a useful prognostic indicator for prediction of coronary heart disease and cardiovascular events, and is expected to be used clinically as a convenient diagnostic method for coronary heart disease. However, the ability of this score to predict the risk of coronary heart disease has not been clarified in relation to ethnicity and other patient background factors (note: ASGES is not intended for patients with diabetes mellitus), so further research is warranted.

2.2.4 Genetic Risk Score

Recent advances in genome-wide association studies have led to the discovery of a number of genetic markers associated with coronary heart disease, including various single-nucleotide polymorphisms, based on which attempts have been made to calculate a genetic risk score for coronary heart disease. The score for genetic factors is associated with coronary heart disease independent of conventional risk factors, and it is expected that combining assessment of genetic factors with conventional risk factors, including the family history, may lead to improved prediction of the
risk of coronary heart disease. However, further development of analytical methods, including accumulation of more evidence and obtaining specific data for Japan, is needed before use in the clinical setting will become possible. Recommendations and levels of evidence for additional risk factors and biomarker are shown in Table 47.

### 3. Familial Hypercholesterolemia

FH is one of the most common inheritable diseases. It features a triad of elevated LDL-cholesterol (LDL-C), tendinous xanthomas, and coronary atherosclerosis, and FH patients have an increased risk of premature death from early-onset coronary artery disease. FH is also common among patients with coronary heart disease, and a diagnosis of FH is essential for sufficient risk management and for cascade screening of the patient’s family.

#### 3.1 Clinical Features

##### 3.1.1 Epidemiology

FH is caused by LDL-receptor dysfunction and shows autosomal dominant inheritance, with the exception of rare cases of autosomal recessive hypercholesterolemia (ARH). There are 2 types of FH: heterozygous with 1 causative gene mutation and homozygous with 2 causative gene mutations with severe phenotype. Heterozygous FH were once thought to be a prevalence of 1 in 500 of the general population; however, recent advances in molecular genetics have suggested a much higher prevalence of 1 in 200–300 in many countries, including Japan.

As a matter of course, FH is more common among patients with hyperlipidemia or coronary heart disease than among healthy persons. One national survey showed that 3.4% of patients who visited medical institutions because of elevation of LDL-C had FH. Tendinous xanthomas are a highly specific physical finding for FH, and have been reported to be present in approximately 10–20% of patients with ACS in Japan.

Table 47. Recommendations and Levels of Evidence for Additional Risk Factors and Biomarkers

<table>
<thead>
<tr>
<th>Risk Factor/Marker</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taking a family history</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>Urate-lowering therapy</td>
<td>Ila</td>
<td>A</td>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td>CPAP for obstructive sleep apnea</td>
<td>Ila</td>
<td>A</td>
<td>B</td>
<td>II</td>
</tr>
<tr>
<td>Exercise therapy</td>
<td>I</td>
<td>A</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Alcohol intake control</td>
<td>Ila</td>
<td>C</td>
<td>C1</td>
<td>VI</td>
</tr>
<tr>
<td>Influenza vaccination</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>II</td>
</tr>
<tr>
<td>Consideration of psychological aspects</td>
<td>Ila</td>
<td>C</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>Consideration of social aspects</td>
<td>I</td>
<td>C</td>
<td>C1</td>
<td>VI</td>
</tr>
<tr>
<td>Use of inflammatory markers as predictors of coronary heart disease</td>
<td>Ila</td>
<td>B</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>Use of lipid-related/myocardial necrosis markers as predictors of coronary heart disease</td>
<td>Iib</td>
<td>B</td>
<td>C1</td>
<td>IVa</td>
</tr>
<tr>
<td>Use of ASGES* as a predictor of coronary heart disease</td>
<td>Iib</td>
<td>C</td>
<td>C1</td>
<td>IVa</td>
</tr>
<tr>
<td>Use of genetic risk scores* as a predictor of coronary heart disease</td>
<td>Iib</td>
<td>C</td>
<td>C1</td>
<td>IVa</td>
</tr>
</tbody>
</table>

*There is little evidence for the Japanese population, so clinical application may be appropriate in the future. ASGES, Age- and Sex-Specific Gene Expression Score; COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

An international study on the diagnosis rate of FH showed that more than 70% of FH patients were diagnosed in the Netherlands, with diagnosis rates generally being high in Europe, while Japan was one of the countries with a very low diagnosis rate of <1%. Improving the diagnosis rate of FH among patients with coronary heart disease is a pressing issue. Although only a few cases of ARH have been reported in Japan, it should be suspected in FH patients without a distinct family history.

##### 3.1.2 Hyper-LDL Cholesterol

The number of FH gene mutations is related to the cholesterol level, with total cholesterol being 179±26 (mean±SD [mg/dL]) in normal family members of FH patients, 338±63 in heterozygous FH, and 713±122 in FH homozygotes. Thus, the cholesterol level is approximately 2-fold that of normal subjects in heterozygous FH and 4-fold more in homozygous FH (Figure 19). A national survey conducted by the Research Committee on Primary Hyperlipidemia of the Ministry of Health, Labour, and Welfare of Japan revealed that the mean LDL-C level was 248 mg/dL in 641 untreated FH homozygotes (296 men and 345 women; mean age: 51 years), showing no sex difference.

Hyper-LDL cholestrolemia is not specific to FH, and there is considerable overlap in the distribution of LDL-C
levels between non-FH patients and FH heterozygotes (Figure 19). According to the diagnostic criteria of the Japan Atherosclerosis Society (Table 48), the threshold LDL-C level is ≥180 mg/dL in adults (≥15 years), based on a balance between sensitivity and specificity. However, the multicenter study for this criterion showed that approximately 5% of FH patients revealed LDL-C <180 mg/dL. Therefore, FH should not be ruled out simply because LDL-C is <180 mg/dL. Mabuchi et al reported that the optimal cutoff LDL-C level for the diagnosis of definite FH was 160 mg/dL based on genetic diagnosis, indicating that FH should be suspected when LDL-C is ≥160 mg/dL in adults. In addition, the LDL-C level is ≥140 mg/dL with a family history of FH in the diagnostic criteria for pediatric FH. Thus, detection of xanthomas and a positive family history are more important for diagnosis of FH than LDL-C, which is less specific.

### 3.1.3 Tendinous Xanthomas, Cutaneous Xanthomas, and Arcus Corneae

**a. Tendinous Xanthomas**

Tendinous xanthomas are pathognomonic for FH and most often affect the Achilles tendon (Figure 20). Tendinous xanthomas are thickenings of tendons due to cholesterol deposits, and FH patients with apparent tendinous xanthomas tend to have more severe coronary artery lipidemia. Although an experienced physician can identify xanthomas by palpation, measuring the Achilles tendon thickness on a lateral X-ray film is quite useful. Typically, the middle portion that is normally the thinnest part of the Achilles tendon becomes thickened and spindle-shaped, and a width ≥9 mm defined as significant thickening. The Achilles tendon should be measured by carefully determining the distance between the borders of the tendon, not including subcutaneous tissues. Tendinous xanthomas may also develop in the dorsum extensor tendon and elbow joints, so these joints should be flexed to detect the presence of xanthomas.

**b. Cutaneous Xanthomas**

Homozygous FH characteristically develop cutaneous xanthomas during infancy, when tendinous xanthomas are usually absent. Cutaneous xanthomas may also occur during infancy in sitosterolemia, so patients with cutaneous xanthomas should be referred to a lipidologist. It should be noted, however, that palpebral xanthomas (xanthelasma palpebrarum) have a low specificity and are not useful for a diagnosis of FH, because these xanthomas also can be found with normolipidemia.

**c. Arcus Corneae**

Arcus corneae is found in ≤30% of heterozygous FH under 50 years of age. It initially appears in the 12 o’clock or 6 o’clock direction and may extend to eventually become circumferential. It is difficult to distinguish arcus corneae from arcus senilis, which is common in adults.

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**Table 48. Diagnostic Criteria for Heterozygous FH in Adults (15 Years of Age or Older)**

- Hyper-LDL-cholesterolemia (an untreated LDL-C level ≥180 mg/dL)
- Tendon xanthomas (thickening of tendons on dorsal side of the hands, elbows, knees or Achilles tendon hypertrophy) or xanthoma tuberosum
- Family history of FH or premature CAD (within the patient’s second-degree relatives)

- The diagnosis should be made after excluding secondary dyslipidemia.
- If a patient meets two or more of the above-mentioned criteria, the condition should be diagnosed as FH. In case of suspected heterozygous FH, making a diagnosis using genetic testing is desirable.
- Xanthelasma is not included in xanthoma tuberosum.
- Achilles tendon hypertrophy is diagnosed if the Achilles tendon thickness is ≥9 mm on X-ray imaging. (See Appendix of the source document.)
- An LDL-C level of ≥250 mg/dL strongly suggests FH.
- If a patient is already receiving drug therapy, the lipid level that led to treatment should be used as the reference for diagnosis.
- Premature CAD is defined as the occurrence of CAD in men <55 years of age or women <65 years of age, respectively.
- If FH is diagnosed, it is preferable to also examine the patient’s family members.
- These diagnostic criteria also apply to HoFH.

CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol. (Reproduced from Kinoshita et al 2018, with permission.)
elderly persons. However, if a person younger than 50 years old has obvious arcus cornea, it should be considered as a physical finding associated with FH.

### 3.1.4 Early-Onset Coronary Atherosclerosis and Risk of Recurrence

Male FH heterozygotes can develop acute myocardial infarction from around the age of 30 years, whereas female FH heterozygotes do so from around age 50. Before the widespread use of strong statins, 60% of FH patients died of cardiovascular disease. According to Tada et al, CCTA shows development of coronary plaques from ≈20 years of age in male FH patients and from ≈30 years in female FH patients. In an overseas cohort study, Nordestgaard et al reported a 13-fold increase in cardiovascular risk in patients with FH who were not taking statins. Moreover, Mundal et al reported an 8-fold increase in the risk of cardiovascular death in FH patients aged 20–39 years and increased risk of premature mortality, despite the fact that lipid-lowering drugs tend to be prescribed proactively in FH patients. According to Perak et al, the onset of cardiovascular disease was respectively accelerated by 10–20 years in men and 20–30 years in women with FH lipid phenotype. The prognosis of FH patients can be improved by early diagnosis and early initiation of cholesterol-lowering treatment.

Even under secondary prevention of coronary heart disease, FH increases the risk of recurrent events. Nanchen et al reported that the risk of recurrent coronary events during 1 year after hospitalization for ACS was about twice as high in patients with FH than in patients without FH, despite the mean age of the FH patients being at least 10 years younger and use of high-dose statin therapy. In Japan, tendinous xanthomas are found in 10–20% of patients with ACS, and such patients should be screened for FH and given appropriate treatment.

### 3.2 Diagnosis

#### 3.2.1 Clinical Diagnosis

**a. Adults**

The diagnostic criteria of the Japan Atherosclerosis Society are shown in Table 48. Tendinous xanthomas are extremely rare in persons without FH, and FH can be diagnosed if elevation of LDL-C is accompanied by detection of tendinous xanthomas. Because family members may have already died of coronary artery disease, especially in males, a family history of early-onset coronary arteriosclerosis (<55 years for men and <65 years for women) is currently considered to indicate FH among a patient’s relatives.

**b. Homozygous FH**

Patients with homozygous FH have a very poor prognosis, because coronary atherosclerosis, supravalvular aortic stenosis, etc. progress from childhood, and cardiovascular death before adulthood is not rare if FH is not sufficiently treated. The clinical diagnosis of homozygous FH is made when both parents are homozygous FH, the LDL-C level is approximately twice that in homozygous FH (LDL-C often >500 mg/dL), and cutaneous xanthomas occur from infancy. When homozygous FH is suspected, early referral to a lipidologist should be considered. Homozygous FH
is under the category of Designated Intractable Diseases covered under the Japanese National Health Insurance system for medical financial support. Genetic diagnosis can be the scientific evidence of diagnosis for the application for subsidies.

### 3.2.2 Genetic Diagnosis
Gene mutations are confirmed in 60–80% of patients with a clinical diagnosis of FH. Mutations of the LDLR gene represent the most common cause of FH. In Japan, ≈5% of FH is caused by mutations of the PCSK9 gene. Tada et al reported an additive effect of positive clinical signs such as tendinous xanthoma of FH and positive FH mutation status to coronary artery disease risk among patients with significantly elevated LDL-cholesterol. In addition, APOB gene mutations have been attributed to a significant portion of FH in Caucasians. One allele mutation in the LDLR, PCSK9, or APOB genes causes heterozygous FH as an autosomal dominant pattern of inheritance, and mutations in both alleles in these genes causes homozygous FH. Double heterozygotes with mutations of the LDLR and PCSK9 genes may not show simple Mendelian inheritance. ARH is caused by mutations of the LDLRAP1 gene and shows recessive inheritance, so only homozygotes (or compound heterozygotes) will develop the clinical phenotype of homozygous FH.

In addition, a considerable number of patients who have been considered as severe heterozygous FH with an LDL-C level of ≈400 mg/dL are found to be homozygous by genetic analysis. The genetic diagnosis can provide important information on the potential response to drug therapy, prognosis, and treatment strategies, especially in severe cases. However, genetic diagnosis of FH is not covered by public health insurance at present.

### 3.2.3 Suspected FH
It is important to be aware of the possibility of FH during diagnosis and drug therapy, as it is impossible to make a definite diagnosis for all patients with suspected FH. At present, there is no definition of “suspected FH” in the diagnostic guideline of the Japanese Atherosclerosis Society, but examination and risk management for coronary atherosclerosis should be handled in a similar way to FH, particularly in patients with a family history of hyperlipidemia or coronary artery disease and patients with high LDL-C levels.

### 3.2.4 Differential Diagnosis
#### a. Other Diseases Associated With Xanthomas
In addition to ARH, sitosterolemia can be considered in infants with cutaneous xanthomas and elevation of LDL-C (to the same degree as in homozygous FH) whose parents do not have hyper-LDL cholesterolemia. Cerebro-

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**Figure 21.** Radiographic imaging of an Achilles tendon xanthoma. (Reproduced from Nohara A, 2017, and Mabuchi H, 2005, with permission.)
plasma cholestanol level and prominent tendinous xanthomas disproportionate to the LDL-C level.

### 3.3 Lipid Management

#### 3.3.1 Lipid Management Targets for Primary and Secondary Prevention

FH is a high-risk disease for coronary heart disease, and lipid-lowering therapy should be started at the same time as guidance on lifestyle modification and optimum body weight (Figure 22). The target LDL-C level is <100 mg/dL or <50% of the untreated LDL-C level for heterozygous FH as primary prevention therapy, and is <70 mg/dL for both heterozygotes and homozygotes in secondary prevention therapy. As dietary therapy for FH, patients should be instructed as follows: (1) keep the intake of saturated fatty acids from 4.5% to 7%, (2) reduce the intake of trans-fatty acids, and (3) keep cholesterol intake to ≤200 mg/day.

#### 3.3.2 Selection of Drugs

Statins are the first-line drug therapy, and efficacy of statin therapy for preventing cardiovascular events in FH patients has been reported in Japan and overseas. Strong statins should be used, together with ezetimibe, resins (bile acid sequestrants), etc., but it is often difficult to maintain LDL-C <70 mg/dL in FH patients for secondary prevention. PCSK9 inhibitors can further reduce LDL-C levels by ≈60% in FH heterozygotes already on treatment with existing therapies such as statins, and reduce Lp(a) as well. The FOURIER study of patients with a high risk of coronary heart disease showed that evolocumab reduced cardiovascular events. In the ODYSSEY OUTCOME study investigating post-ACS patients, alirocumab reduced cardiovascular events and all-cause death. From the perspective of medical economics, PCSK9 inhibitors should be indicated for FH patients for the secondary prevention of coronary heart disease who show an insufficient response to the maximum tolerable doses of statins combined with ezetimibe.

#### a. Treatment Algorithm for Heterozygous FH

Strong-statin-based therapy should be initiated, combined with ezetimibe as needed, and additional drugs may be considered if the response to these medications is insufficient. Particularly, PCSK9 inhibitors should be considered when necessary, especially for FH patients in secondary prevention (Figure 22). LDL-apheresis may also be considered in the secondary prevention for patients who do not respond sufficiently to PCSK9 inhibitors. However, homozygous FH should be suspected in such patients.
and genetic diagnosis should be strongly considered.

b. Treatment Algorithm for Homozygous FH
The prognosis is poor and if the response to current treatment is insufficient, more aggressive treatment should be considered (Figure 23). Statins and PCSK9 inhibitors are dependent on LDL-receptor activity and are often less effective or ineffective for homozygous FH. The degree of LDL-C reduction with these drugs can be achieved according to the residual LDL-receptor activity.

LDL-apheresis is still a mainstay of treatment for homozygous FH. These patients should be managed by combining multiple active treatments. MTP inhibitors are oral drugs that work independent of LDL-receptor activity. Only homozygous FH patients are indicated for MTP inhibitor therapy, which can reduce LDL-C levels by half. However, gastrointestinal symptoms and hepatosteatosis are common side effects, so MTP inhibitors should be started at a low dose under the guidance of a specialist, together with dietary counseling and restriction of alcohol intake.918

Figure 23. Algorithm for treatment of adult (15 years of age or older) FH homozygotes. LDL-C, low-density lipoprotein cholesterol. (Reproduced from Kinoshita et al 2018,4 with permission from the Japan Atherosclerosis Society. https://www.jstage.jst.go.jp/article/jat/25/9/25_GL2017_pdf/-char/en)

<table>
<thead>
<tr>
<th>Table 49. Recommendations and Levels of Evidence for FH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FH should be suspected in patients with premature coronary heart disease (men &lt;55 years old and women &lt;65 years old)</strong></td>
</tr>
<tr>
<td><strong>Presence of tendinous xanthomas should be checked in all patients with coronary heart disease</strong></td>
</tr>
<tr>
<td><strong>High-intensity statins are the first choice for LDL-C-lowering therapy in FH, and combination with ezetimibe should be considered when required</strong></td>
</tr>
<tr>
<td><strong>In secondary prevention for patients with FH, an LDL-C goal of &lt;70 mg/dL is recommended, and appropriate combination therapy should be considered when necessary</strong></td>
</tr>
<tr>
<td><strong>If FH is diagnosed, it is preferable to also examine the patient’s family members</strong></td>
</tr>
</tbody>
</table>

COR, class of recommendation; GOR, grade of recommendation; LDL-C, low-density lipoprotein cholesterol; LOE, level of evidence.

3.4 Diagnosis and Treatment of Family Members
An early diagnosis and treatment are essential to prevent premature death in FH patients, but the diagnosis rate is extremely low in Japan.887 Therefore, many undiagnosed cases are suspected to exist in a family with FH. In fact, there is a 50% chance that parents and siblings may have FH. Accordingly, when a diagnosis of FH is made, the physician should also advocate testing and treatment for family members.

3.5 Future Challenges
More aggressive lipid-lowering therapy is required for FH
patients than for non-FH patients, and it is particularly important to sufficiently reduce the LDL-C level in secondary prevention. In patients with chronic coronary heart disease, it is important to diagnose and treat FH adequately, together with an early diagnosis and treatment of family members. Recommendation and levels of evidence for diagnosis of FH are shown in Table 49.

### III. Selecting Tests for Chronic Coronary Heart Disease Based on the Pathological Condition and Diagnostic Objectives

#### 1. Diagnosis of Myocardial Ischemia

Investigation of myocardial ischemia is essential for diagnosing and assessing the severity of chronic coronary heart disease. Making a choice from among pharmacological therapy, PCI, or CABG requires quantitative assessment of regional myocardial ischemia, rather than anatomical coronary artery stenosis. Stress testing is usually done to detect the existence of myocardial ischemia, except when it is contraindicated. Exercise stress ECG is widely used for noninvasive testing, because it is simple and cost-effective and can evaluate the severity of ischemia, exercise tolerance, and the prognosis. However, exercise stress ECG does not always have a high sensitivity and specificity for diagnosing the culprit vessels causing ischemia and the ischemic regions.

Accordingly, stress myocardial perfusion imaging and stress echocardiography are used when exercise cannot be performed or when diagnosing ischemia by ECG is found to be difficult. In recent years, the use of CCTA has been increasing rapidly. In high-risk patients who are considered to have severe myocardial ischemia based on symptoms and the results of noninvasive testing, coronary angiography should be performed in anticipation of coronary revascularization. Coronary angiography is invasive, but essential to confirm the diagnosis of coronary heart disease and determine the need for revascularization.

Whether coronary angiography is performed should be decided by comprehensive assessment of the clinical findings, laboratory findings, and the patient’s wishes. The prevalence of patients with vasospastic angina is higher in Japan than in Western countries, and the pathophysiology of this condition differs from that of effort angina. Therefore, performing Holter ECG and coronary spasm provocation testing are required for diagnosis.

It is desirable to select the most appropriate examination from among various modalities for evaluating myocardial ischemia, according to the purpose. The diagnostic algorithm for myocardial ischemia (Figure 24) is set out below. For the details of each test, see the relevant sections of this Guideline. With regard to FFR-CT, HeartFlow FFR-CT has been covered by health insurance in Japan as of December 2018. However, the number of facilities that can perform this test is limited and further evidence needs to be accumulated. Accordingly, FFR-CT has not been included in the algorithm.

#### 1.1 Initial Assessment of Clinical Findings

It is important to estimate the probability of the existence of coronary heart disease (pretest probability) from clinical findings such as the patient’s history and coronary risk factors. It is important to estimate the probability of the existence of coronary heart disease (pretest probability) from clinical findings such as the patient’s history and coronary risk factors.

### 1.1.1 History

Taking an accurate history is the most important starting point for the diagnosis of angina pectoris. The history is also important for understanding the patient’s social background and personality, establishing a relationship of trust with the patient, and obtaining informed consent.

#### a. Symptoms

Information should be collected about the site, nature, duration, onset, and offset of chest symptoms (pain, etc.), as well as associated symptoms. The sites of symptoms include the mid-precordial region, left anterior chest, and epigastrium, with the most common site being the mid-precordial region. Symptoms generally affect an appreciable area, so localized symptoms such as those indicated by a single finger are unlikely to be due to coronary heart disease.

Symptoms often radiate to the neck, throat, jaw, arms, shoulders, and back, and may also be confined to any of these areas. Patients often describe a feeling of oppression, squeezing, or leadenness, and shortness of breath may be the chief complaint of patients with severe ischemia. A sharp pain, commonly described as tingling or throbbing, is unlikely to be related to coronary heart disease.

The duration of symptoms is often a few minutes or less, and symptoms may be induced by physical exertion, mental agitation, cold exposure, etc. If provoked by exertion, symptoms resolve within minutes of stopping exertion and use of a rapid-acting nitrate preparation. Women, elderly persons, and patients with diabetes mellitus often have atypical symptoms. Also, elderly persons, patients with diabetes mellitus, patients with a history of myocardial infarction, and patients who have undergone surgical coronary revascularization tend to have asymptomatic myocardial ischemia. Therefore, history taking should be done carefully for these patients.

#### b. Medical History and Oral Medications

Information should be collected about the presence and management of diabetes mellitus, hypertension, and dyslipidemia, the presence/absence of smoking (current or prior), a family history of coronary heart disease, and oral medications. See Chapter II of this Guideline for details of these coronary risk factors.

#### 1.1.2 Physical Findings

Physical findings are not noteworthy in many patients. In patients with severe ischemia, however, a gallop rhythm or systolic regurgitant murmur may be audible by auscultation during attacks because of decreased left ventricular wall motion and mitral regurgitation. Physical findings are important for differentiation from other diseases that can cause thoracic symptoms (periarterial disease, heart failure, pulmonary/plural disease, pulmonary embolism, gastrointestinal disease, musculoskeletal disease, etc.).
1.1.3 Standard 12-Lead ECG

Standard 12-lead ECG is the most convenient and basic diagnostic test for coronary heart disease in daily clinical practice. In patients with angina symptoms or having an angina attack, 12-lead ECG should be recorded. However, the ECG may be normal during the intervals between angina attacks in patients with stable angina. Therefore, coronary heart disease cannot be ruled out by a normal resting ECG in these patients.921

The diagnosis of myocardial ischemia is mainly based on detection of ST-T changes. However, the ST-segment and T wave can be affected by a wide range of conditions, including cardiac hypertrophy, intraventricular conduction defects, myocardial disease, electrolyte abnormalities, drugs such as digitalis preparations, and autonomic activity.922,923

Differentiation between changes caused by these conditions and myocardial ischemia is often difficult and requires comprehensive assessment of the history, clinical findings, and other laboratory results.

a. ST Elevation

ST elevation suggests transmural ischemia caused by complete occlusion of the culprit coronary artery.922 and ST elevation is observed in leads facing the site of transmural...
ischemia. However, ST elevation can also be seen as an electrocardiographic finding in normal individuals. The normal ST level varies with age, sex, and the ECG leads. In general, it is highest in leads V2–3, and higher in men than in women.924 According to an international definition,924 ST elevation is electrocardiographic evidence of acute myocardial ischemia if it occurs in ≥2 contiguous leads and has the following characteristics: ST elevation ≥0.20 mV in leads V2–3 in men aged 40 years or older, ST elevation ≥0.25 mV in leads V2–3 in men under 40 years old; ST elevation ≥0.15 mV in leads V2–3 in women of any age; or ST elevation ≥0.1 mV in leads other than V2–3. (This definition applies in the absence of left ventricular hypertrophy or left bundle branch block, and the ST level is measured at the J point.)

b. ST Depression
ST depression is the most important electrocardiographic evidence of subendocardial ischemia. However, it is difficult to diagnose the culprit vessel on the basis of ST depression (unlike ST elevation), because ST depression generally occurs in leads V4–6 regardless of the culprit coronary artery. The extent of myocardial ischemia increases as ST depression becomes deeper, involves a larger number of leads, or becomes longer.

In daily clinical practice, an ECG diagnosis is often done by using 11 leads and excluding aVR. However, aVR is a useful lead for the diagnosis of extensive ischemia of the left ventricular endocardium because it looks into the left ventricular cavity from the right shoulder. Severe ischemia because of left main trunk disease or multivessel disease can be suspected in the case of ST elevation in lead aVR combined with widespread ST depression.925

c. Negative T Wave
Negative T waves are considered to reflect abnormal repolarization of the ischemic myocardium and are a representative electrocardiographic finding together with ST depression.

d. Negative U Wave
Negative U waves are a highly specific electrocardiographic finding that suggests severe myocardial ischemia when they occur transiently during an ischemic attack or during exercise testing, and thus have high diagnostic significance. Negative U waves occur in leads facing the site of ischemia, and negative U waves centered on leads V3–5 suggest a left anterior descending artery lesion.926 Because the negative U wave is a shallow and small wave following the T wave, it is important to form a diagnosis by keeping in mind that negative U waves may appear at the time of ischemia. On the other hand, negative U waves can be observed when the blood pressure is elevated or in patients with conditions such as aortic valve regurgitation. Hence, a diagnosis of myocardial ischemia should be made in consideration of other clinical findings.

e. Abnormal Q Wave
The presence of abnormal Q waves contributes to a diagnosis of myocardial infarction.922 However, because isolated Q waves in lead III and a QS patterns in lead V1 may be seen in normal persons,922 the diagnosis must be made in conjunction with the history, clinical findings, and other laboratory results.

1.1.4 Chest X-ray
Chest X-ray findings are often normal in patients with stable angina. However, abnormalities may be detected in patients with a history of myocardial infarction, patients with other types of heart disease, or patients with pulmonary/pleural disease or skeletal disease who complain of chest symptoms attributable to causes other than coronary heart disease. An enlarged cardiac silhouette suggests a history of myocardial infarction, as well as heart failure, valvular disease, and pericardial effusion. The presence of pulmonary congestion is also an important finding in the diagnosis of severe ischemia.

1.2 Selection of Examination Tests
It is crucial to estimate the pretest probability of coronary heart disease, to select diagnostic tests based on this, and to plan the next diagnostic strategy from the results thus obtained. Stress testing is performed to induce myocardial ischemia and to examine its presence and extent. However, stress testing is contraindicated in patients with ACS in principle, and patients must be monitored for changes in symptoms or resting ECG findings at the time of appointment or before testing.

1.2.1 Exercise ECG
Exercise ECG is widely used for the diagnosis of myocardial ischemia because it is simple, cost-effective, and allows both assessment of exercise tolerance and evaluation of the prognosis. However, there are some limitations to its indications because patients must be able to perform exercise and because the diagnosis of ischemia on the ECG must be possible, including the absence of conditions causing ST-T abnormalities on the resting ECG such as Wolff-Parkinson-White (WPW) syndrome or left bundle branch block. It is important to keep the pretest probability in mind when making a diagnosis.

For elderly men who have multiple coronary risk factors and typical clinical features of effort angina, exercise testing with continuous recording of the ECG and blood pressure monitoring is recommended. If the test is positive, there is a high probability that the patient has coronary heart disease (true-positive result). If the test is negative, the possibility of a false-negative result should be considered. In contrast, young and middle-aged adults often have normal coronary arteries even when the exercise ECG shows abnormalities (false-positive result).927 Thus, diagnosis of ischemia should be made by comprehensive assessment, and not solely from the exercise ECG.928

Exercise testing is not only useful for diagnosing myocardial ischemia, but also for estimation of the prognosis. A larger number of lesions, higher frequency of ST depression, ST depression ≥0.2 mV, onset of ST depression at a low exercise load, poor blood pressure response to exercise, and poor exercise tolerance are all negative prognostic indicators.5,28,30,31,929,930 When treadmill exercise ECG is performed, risk stratification is possible by calculating the Duke treadmill score from the duration of exercise loading, maximum ST depression, and chest symptoms as follows: (exercise duration) – 5 × (maximum ST depression in mm) – 4 × (angina pectoris score: 0 for no angina symptoms during stress testing, 1 for angina symptoms, and 2 if angina symptoms require cessation of exercise). A score of −11 or less is considered to indicate a high risk, while a score of +5 or more is considered to indicate a low risk.5 If
the risk is low, the prognosis is good and only routine follow-up is required. If the risk is judged to be high, coronary revascularization should be considered and coronary angiography is a priority. If the risk is intermediate or undeterminable, another noninvasive test should be selected for achieving a diagnosis.

Exercise ECG is the noninvasive test of first choice for myocardial ischemia, but it has several limitations. In particular, nonspecific ST depression (≥0.1 mV) on the resting ECG, cardiac hypertrophy, intracardiac conduction abnormalities (bundle branch block, ventricular pacing, WPW syndrome, etc.), use of digitalis preparations, electrolyte abnormalities, and a history of myocardial infarction are known to render this test nondiagnostic (i.e., the result is often undeterminable, or else false-positive or false-negative). Accordingly, other tests should be selected when it is difficult to diagnose ischemia by ECG or if exercise is considered to be contraindicated or inappropriate (elderly patients, patients with aneurysms, PAD, etc.). For the performance of exercise ECG, see the sections describing the individual methods in this Guideline.

### 1.2.2 Selection of Other Noninvasive Tests

Noninvasive tests that may follow or replace exercise ECG include stress echocardiography,\(^{211-213}\) which can evaluate physiologic and functional myocardial ischemia, and stress myocardial perfusion imaging modalities such as stress myocardial perfusion scintigraphy, MRI, CT, or PET.\(^{226-227,265,267,300-305}\) These tests have a high level of diagnostic usefulness when the pretest probability (mentioned above) is considered to be intermediate. The advantages of stress echocardiography over stress myocardial perfusion imaging are that it is simple and does not require expensive equipment, large facilities, or radiopharmaceuticals for which particular caution needs to be exercised. Disadvantages include the difficulty of recording good images in some patients and high dependency of the results on the skill of the operator. On the other hand, stress myocardial perfusion scintigraphy shows high diagnostic accuracy for evaluation of myocardial ischemia without needing contrast medium, and is therefore widely used in daily clinical practice. In addition to the presence of myocardial ischemia, the extent and severity of myocardial ischemia can be examined, and there is abundant evidence for its use in prognostic evaluation.\(^{226,227,262,300,305-307}\)

However, it is a relative method of evaluation based on the difference in blood flow between normal and ischemic myocardium, so there are limitations for detecting ischemia in patients with severe and extensive myocardial ischemia, such as those with multivessel disease or left main trunk lesions. Other disadvantages are relatively high radiation exposure and low image resolution, making it impossible to perform a morphological evaluation of the coronary arteries. Stress myocardial perfusion imaging with PET achieves superior image quality to SPECT, but it is only covered by health insurance for diagnosis of myocardial ischemia that is difficult to determine by other modalities. The radionuclide used for myocardial perfusion PET is N-13 ammonia, which has a short half-life of 10 min and is only available at a limited number of facilities where it can be synthesized. On the other hand, stress myocardial perfusion MRI does not involve radiation exposure and has a high spatial resolution allowing clear delineation of subendocardial ischemia and diffuse myocardial ischemia caused by multivessel disease.

It has been reported to show better diagnostic performance than stress myocardial perfusion scintigraphy.\(^{265,997}\) However, it is not widely used because of problems such as the complexity of the test, long imaging time, and high level of skill required for interpretation. CCTA has high accuracy for detecting coronary artery stenosis\(^{899-941}\) and can be performed rapidly with low invasiveness, so there has been a dramatic increase in its use in recent years. In addition, CT stress myocardial perfusion imaging can be done to assess myocardial ischemia by observing contrast staining of the myocardium after drug administration. It has been reported to be useful as an auxiliary method for the diagnosis of lesions that cannot be evaluated on CCTA and lesions with moderate or severe stenosis, because it has a similar diagnostic performance to SPECT or MRI for detecting stenotic vessels and myocardial ischemia. Thus, the noninvasive tests that can follow or replace exercise ECG are morphological evaluation with CCTA, stress myocardial perfusion imaging (SPECT, MRI, CT, and PET), or stress echocardiography to evaluate myocardial ischemia.

The choice of modality will depend on the estimated pretest probability for coronary heart disease, the institution (whether the diagnostic accuracy of a given test is adequate at each institution), and the patient (is the test sufficiently indicated in a given patient). Regarding the patient, adequate consideration should be given to contraindications and the risks/side effects of testing. Noninvasive diagnosis of myocardial ischemia is important when determining the indications for invasive coronary angiography and coronary revascularization, and evaluation of myocardial ischemia by stress myocardial perfusion SPECT is well documented and it is often the method of first choice.

In the case of stress myocardial perfusion scintigraphy showing that coronary artery stenosis is not functionally significant, the prognosis is good and the patient is followed up routinely. Performing CCTA may be considered if mild perfusion abnormalities are present or if the result is undeterminable. On the other hand, moderate or severe abnormalities on stress myocardial perfusion scintigraphy indicate a high risk, so coronary angiography should be performed in anticipation of coronary revascularization.

CCTA has a high negative predictive value and is excellent for exclusion diagnosis.\(^{941}\) If CCTA gives a normal result, coronary artery disease can be almost completely ruled out and the patient should be followed up. Even if CCTA shows mild abnormalities, the patient should be followed up because myocardial ischemia is unlikely. If significant stenosis is detected, CCTA only provides an anatomical assessment, so whether coronary revascularization is required should be determined by other diagnostic methods that can confirm the presence of myocardial ischemia. Nevertheless, if a severe stenosis is found that seems clearly indicated for coronary revascularization, coronary angiography should be performed next. On the other hand, when judgment by CCTA is difficult because of severe calcification, motion artifacts, borderline stenosis, etc., myocardial ischemia can be assessed by other modalities. More recently, fusion imaging with CCTA and myocardial blood flow SPECT have been developed, allowing simple and accurate detection of the culprit coronary artery by utilizing the advantages of morphological and functional imaging.\(^{421}\) Improvements in both are expected in the future. See the sections describing the individual tests in this Guideline for details of each test.
### 1.3 Diagnosis of Myocardial Ischemia in Patients With Vasospastic Angina

Vasospastic angina is more common among Japanese patients than in Westerners.\(^6\) Because the mechanisms underlying onset, pathology, and clinical features differ between vasospastic angina and stable effort angina, the methods used for diagnosis of myocardial ischemia are also different. In patients with stable effort angina, significant coronary stenosis exists and causes myocardial oxygen demand to exceed oxygen supply on exertion, giving rise to myocardial ischemia. Therefore, exercise testing is useful for diagnosis of myocardial ischemia in these patients. On the other hand, coronary blood flow is decreased by functional coronary artery occlusion or stenosis stemming from coronary spasm in patients with vasospastic angina, resulting in myocardial ischemia. Vasospastic angina often occurs at night or in the early morning. Therefore, its diagnosis requires Holter ECG and a coronary spasm provocation test. The detailed diagnosis of vasospastic angina has been described in the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina (revised in 2013),\(^6\) so this section provides brief information.

#### 1.3.1 Symptoms

Although the symptoms do not differ from those of effort angina, an attack of vasospastic angina has the following characteristics: (1) particularly occurs while resting at night or in the early morning (often during sleep) and is not usually induced by daytime exercise, but can be induced by mild exertion in the early morning, so there is clear diurnal variation; (2) may be induced by hyperventilation or alcohol; (3) rapid-acting nitrates are highly effective for controlling attacks and calcium antagonists are effective for prevention; and (4) attacks are often accompanied by arrhythmias and disturbance of consciousness or loss of consciousness may occur if there is associated complete atrioventricular block, ventricular tachycardia, or ventricular fibrillation.\(^4\)

#### 1.3.2 Standard 12-Lead ECG

ECG is often normal in the absence of an attack. However, a definitive diagnosis can be made by recording and comparing 12-lead ECGs during an attack and in the normal state. The most typical electrocardiographic finding during an attack is ST elevation in the leads facing the site of coronary spasm,\(^8\) whereas negative T waves are often seen as the myocardium is recovering from ischemia. However, electrocardiographic changes depend on the severity of coronary spasm and may include ST depression or appearance of new negative U waves.\(^5\)

#### 1.3.3 Holter ECG

About 20–30% of patients with vasospastic angina have chest symptoms associated with ST changes and asymptomatic coronary spasm is common. Because attacks often occur while resting at night or in the early morning and are sometimes associated with arrhythmias, Holter ECG is a highly useful diagnostic test.\(^6\) Multichannel or 12-lead Holter ECG should be recorded rather than 2-channel ECG whenever possible. The possibility of capturing the electrocardiographic changes during an attack increases as the recording time becomes longer.

#### 1.3.4 Coronary Spasm Provocation Testing

The major methods of inducing coronary spasm are noninvasive hyperventilation (breathing at a rate of approximately 30 breaths/min for several minutes)\(^8\) and invasive pharmacological stress testing, which requires intracoronary infusion of acetylcholine or ergonovine using cardiac catheterization. Sufficient consideration is required when performing a coronary spasm provocation test, especially in patients at risk of syncope or severe arrhythmia. See the relevant sections of this Guideline for more details.

#### 1.3.5 Diagnostic Algorithm

For a diagnosis of vasospastic angina, refer to the diagnostic algorithm in the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina (revised in 2013).\(^6\) Recommendations and levels of evidence for diagnosis of myocardial ischemia are shown in Table 50.

<table>
<thead>
<tr>
<th>Table 50. Recommendations and Levels of Evidence for Testing Methods to Assess Myocardial Ischemia in Patients With Suspected Stable Coronary Heart Disease</th>
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<tbody>
<tr>
<td>Test Method</td>
</tr>
<tr>
<td>Exercise testing in patients who can perform exercise and can undergo ECG assessment of ischemia</td>
</tr>
<tr>
<td>Stress imaging in patients who cannot perform exercise or undergo ECG assessment of ischemia</td>
</tr>
<tr>
<td>CCTA in patients who cannot perform exercise or undergo ECG assessment of ischemia</td>
</tr>
<tr>
<td>Coronary angiography in patients clinically judged to be low risk who have not undergone noninvasive assessment of ischemia</td>
</tr>
</tbody>
</table>

CCTA, coronary computed tomography angiography; COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

### 2. Assessment of Coronary Artery Lesions

Assessment of coronary artery lesions is important for the diagnosis, treatment, and prognostication of coronary heart disease. When coronary angiography was the gold standard, it was important to morphologically or functionally assess the severity of coronary artery stenosis. However, it has become clear that vulnerable plaques, which cause ACS and determine the prognosis of coronary heart disease, exist irrespective of the severity of stenosis. Thus, it is important not only to evaluate ischemia but also to identify vulnerable plaques. Because coronary angiography cannot identify vulnerable plaques, intravascular imaging modalities such as IVUS, OCT\(^4\) and angioscopy are required to...
detect vulnerable plaques, as well as providing more accurate morphological assessment of coronary artery stenosis. On the other hand, the diagnostic accuracy of noninvasive MDCT and whole-heart MRA for coronary artery lesions has improved, and morphological information can now be obtained with these modalities, including not only the extent of stenosis but also the presence and properties of plaques. Assessment of ischemia is also important when deciding the treatment of chronic coronary heart disease. Although coronary angiography is still gold standard for assessing stenotic lesions, noninvasive assessment of functional ischemia using Doppler echocardiography or MRI, or alternatively invasive assessment with a Doppler guidewire or pressure guidewire, is required in addition to morphological assessment. Because there is no optimum method at present, it is not desirable to evaluate coronary artery stenosis based on a single method and other evidence of ischemia should also be considered.

Coronary heart disease causes angina pectoris or myocardial infarction due to gradual progression of arteriosclerosis over many years, as well as to rapid formation of thrombi on arteriosclerotic plaques. Progression of coronary artery lesions may not always coincide with the onset of symptoms. Even if coronary artery stenosis progresses, the coronary arteries have an autoregulatory mechanism that may still provide adequate blood flow to meet demand. Thus, angina symptoms only appear after progression of stenosis is severe enough to cause failure of this mechanism. It has been demonstrated that myocardial infarction can also be caused by lesions without severe stenosis. Although there is thus some discordance between symptoms and lesion severity, assessment of coronary artery stenosis is essential to clarify whether symptoms are actually due to coronary heart disease, to determine the severity of the disease, and to select the treatment strategy, including revascularization.

After selective coronary angiography was developed, coronary angiography became the gold standard for investigation of coronary artery stenosis. Currently, it is also possible to evaluate the degree of coronary artery stenosis by noninvasive tests such as MDCT, echocardiography, and MRI. Regarding other invasive tests, the process of vascular remodeling (in which the vessel diameter expands to preserve the intravascular lumen as plaque grows inside the vessel because of arteriosclerosis) has been clarified by advances in intravascular imaging, whereas coronary angiography only evaluates the intravascular lumen and cannot assess such changes. In addition, direct observation of arteriosclerosis lesions by IVUS, OCT, and angioscopy enables determination of the nature of lesions and prediction of ACS. In patients with moderate stenosis whose symptoms cannot be explained by morphological assessment of stenosis, a Doppler guidewire or pressure guidewire can be used to evaluate functional coronary artery stenosis.

### 2.1 Assessment of Coronary Artery Lesions in Chronic Coronary Heart Disease

In patients who have stable effort angina or asymptomatic myocardial ischemia, ischemic changes arise from exertion, irrespective of whether these changes are symptomatic or asymptomatic. This section describes the methods for evaluating coronary artery lesions in patients with stable chronic coronary heart disease.

#### 2.1.1 Targets for Evaluation

In patients with stable symptoms, objective indicators of myocardial ischemia include ischemic ST-T changes on stress ECG, decreased wall motion on stress echocardiography, and decreased blood flow on myocardial perfusion imaging. As the next step, evaluation of coronary artery stenosis is required.

#### 2.1.2 Noninvasive Evaluation

a. CCTA

MDCT has improved the spatial and temporal resolution of CT scans, and the current mainstream 64-row MDCT can be used for definitive diagnosis of coronary heart disease. At present, 320-row MDCT is also available, and equipment with even more improved spatial resolution is being developed. MDCT can be used to assess coronary artery stenosis, patency of coronary stents, or patency of coronary artery bypass grafts and the vessel beyond the anastomosis. It also allows detection of noncalcified coronary artery plaques and assessment of coronary artery remodeling. However, although radiation exposure has been reduced with advances in equipment, it is still problematic to use CCTA for screening.

i) Evaluation of Lesions

Comparison of 64-row MDCT with coronary angiography (gold standard) for detection of significant coronary artery stenosis showed a sensitivity of 82% and 99%, specificity of 64% and 91%, positive predictive value of 64% and 92%, and negative predictive value of 81% and 99%, respectively. Because MDCT has a high negative predictive value, it is particularly useful for exclusion diagnosis, such as when symptoms are atypical or neurocardiac. However, a meta-analysis of randomized studies comparing CCTA and exercise testing in patients with suspected coronary heart disease showed that myocardial infarction was decreased in patients undergoing CCTA, but performance of PCI was increased, with no decrease in hospitalization or death. Unlike coronary angiography, CCTA can visualize the vessel wall and adjacent tissues, enabling preoperative characterization of the lesion. Even if there is total occlusion, visualization of collateral vessels and the course of the occluded vessel is possible, allowing estimation of the feasibility and likely success rate of treatment. In patients with coronary stents, stent fracture can be visualized, in addition to assessment of the lumen. It has recently become possible to evaluate functional coronary artery stenosis with MDCT by calculating the FFR-CT, providing high diagnostic accuracy for the diagnosis of significant CAD, compared with invasive FFR as the reference standard. However, FFR-CT cannot be calculated if a coronary artery has been stented. Among the problems with MDCT, assessment is sometimes difficult in patients who have trouble holding their breath, tachycardia or arrhythmias, or severely calcified lesions.

ii) Assessment of Coronary Artery Calcification

Quantitative assessment of coronary artery calcification by electron-beam CT is useful for predicting coronary artery stenosis and cardiac events. MDCT shows the same accuracy as electron-beam CT, and the extent of calcified stenotic coronary artery lesions is related to coronary stenotic lesions and can be determined with high sensitivity; however, specificity is low.

The ACCF/AHA has stated that quantification of coronary arterioscle-
rosis is useful in asymptomatic intermediate-risk patients for whom the 10-year incidence of cardiovascular events is estimated to be 10–20% based on the Framingham risk score, etc., but quantification of coronary arteriosclerosis is not recommended for low-risk or high-risk patients.  

There are racial differences in the onset and progression of coronary artery calcification. It has been reported that the incidence of coronary artery calcification is lower in Japanese than in American patients, even when their blood pressure and LDL-cholesterol levels are higher. In a Japanese study of 374 patients, the sensitivity and specificity of MDCT for detecting calcified coronary artery stenosis was 75% and 92%, respectively. However, that study included patients who underwent coronary angiography and cannot be used to assess the sensitivity and specificity of MDCT as a screening test.  

A multicenter study performed in 7 countries, including Japan, showed that among patients with suspected symptomatic coronary heart disease, 20% of those with no coronary artery calcification on 64-row MDCT had lesions causing ≥50% stenosis, which indicates that absence of coronary artery calcification does not preclude subsequent coronary angiography in symptomatic patients.

### iii) Assessment of Vulnerable Plaques

MDCT (64-row or more) can be used to assess plaque quality, which cannot be determined by coronary angiography. MDCT identifies vulnerable plaques based on microcalcification, positive remodeling, low CT values, and the napkin-ring sign, as well as showing the extent of stenosis. The napkin-ring sign is a ring-shaped area of high attenuation surrounding a low-attenuation plaque and is an independent predictor of ACS, together with positive remodeling and a low CT value.

### b. Cardiac MRI

Recent advances in technology have been followed by rapid accumulation of evidence that cardiac MRI is useful for both diagnosis and determining the treatment strategies for coronary heart disease. In addition to accurate assessment of cardiac function and regional wall motion by cine MRI, LGE MRI shows higher diagnostic sensitivity for subendocardial infarction than myocardial SPECT. Compared with MDCT, however, the imaging time is longer and spatial resolution is insufficient. Moreover, assessment of the coronary stent lumen is difficult, and cardiac MRI cannot be performed in patients with pacemakers or ICDs that do not support MRI. Still, it is expected to become a useful noninvasive method for assessment of coronary artery lesions without radiation exposure. Recently, some conditionally MRI-compatible ICDs have become available, but safe performance of MRI requires support at accredited facilities and there is a high frequency of images being affected by metal artifacts from the device.

### i) Coronary MRA

Coronary MRA has advantages over cardiac MDCT, including (1) no radiation exposure, (2) no need for contrast agents, and (3) no influence of severe coronary artery calcification on image quality. Whole-heart coronary MRA uses respiratory and electrocardiographic gating to obtain 3-dimensional images of the entire heart. The sensitivity and specificity of coronary MRA for coronary artery stenosis are reported to be 78% and 91–96%, respectively.

In a Japanese multicenter study found a sensitivity of 88%, specificity of 72%, positive predictive value of 71%, and negative predictive value of 88%. It was recently reported that high-intensity lesions on unenhanced T1-weighted images correspond to vulnerable plaques with a low CT value on MDCT, that high-intensity plaques are associated with cardiac events, and that stabilization of plaques by statin therapy can be detected on unenhanced T1-weighted images. These findings have made qualitative assessment of coronary artery plaques by MRI possible.

Coronary MRA is useful for evaluating coronary artery anomalies in young people and coronary artery aneurysms in patients with Kawasaki disease where radiation exposure is a concern. It is also useful for assessment of the coronary arteries in patients with renal failure, because contrast agents are unnecessary. Furthermore, coronary MRA can be performed in patients with severe coronary artery calcification. Accordingly, it is expected to play a role as a screening test instead of coronary angiography in the future. However, stented regions of vessels cannot be visualized, due to metal artifacts, and coronary MRA is therefore unsuitable for assessment of restenosis.

### ii) Stress Myocardial Perfusion MRI

Investigation of myocardial ischemia is important to assess the influence of morphological coronary artery stenosis and to improve the prognosis by performing PCI. When stress myocardial perfusion MRI is performed, a gadolinium contrast agent is administered and the distribution of myocardial blood flow is assessed from the first-pass dynamics of the contrast agent under pharmacological stress such as adenosine. A meta-analysis showed that stress myocardial perfusion MRI had an average diagnostic sensitivity of 89% and specificity of 76% for coronary artery stenosis. In comparison with myocardial SPECT, which is widely used for the diagnosis of myocardial ischemia, stress myocardial perfusion MRI showed excellent diagnostic performance for detection of coronary artery stenosis. In particular, it was significantly superior to myocardial SPECT in patients with multivessel disease.

In a meta-analysis using FFR as the gold standard for functional evaluation of coronary artery stenosis, stress myocardial perfusion MRI was superior to stress myocardial SPECT for detection of significant stenosis.

During the preoperative coronary artery assessment of patients with aortic aneurysms, it is better to avoid coronary angiography because of its risks, but MDCT may not be sufficient for diagnosis, because of severe calcification, suggesting that cardiac MRI may be beneficial in such cases. For assessment of coronary artery lesions by MRI, see the respective methods in this Guideline.

### c. Echocardiography

Echocardiography has advantages such as low cost, no radiation exposure, and able to be performed at the bedside. Its disadvantages include the need to train operators and poor image quality in patients with a certain body size. Typical methods used to diagnose coronary artery lesions are detection of myocardial wall motion abnormality caused by ischemia, and direct visualization of coronary artery stenosis from blood flow velocity signals.

### i) Stress Echocardiography

Unlike stress ECG, stress echocardiography can be performed in patients with ST-segment or T-wave changes on

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the resting ECG caused by digoxin use, left bundle branch block, or left ventricular hypertrophy, and it has a high diagnostic accuracy.\textsuperscript{983} Coronary artery stenosis is diagnosed by detecting left ventricular regional wall motion abnormalities due to myocardial ischemia induced by exercise (treadmill or ergometer) or by pharmacological stress (dobutamine or dipyridamole).\textsuperscript{984} With exercise stress, a standard cross-sectional image is obtained before and immediately after stress loading, and the culprit coronary artery lesion is inferred from the wall motion abnormality in each segment of the left ventricular myocardium. Pharmacological stress can be used in patients who have difficulty performing exercise, and dobutamine challenge is generally performed.\textsuperscript{984} Standard cross-sectional images are recorded before drug infusion, at a low drug dose, at a high drug dose, and after drug infusion in order to diagnose coronary artery stenosis from the changes in wall motion in each myocardial segment.

Investigation of the diagnostic performance of exercise echocardiography has shown a sensitivity of 86\%, specificity of 81\%, and diagnostic accuracy of 85\%.\textsuperscript{983,985} With regard to its performance for diagnosis of significant coronary artery stenosis using dobutamine stress, the sensitivity is 82\%, specificity is 84\%, and diagnostic accuracy is 83\%.\textsuperscript{983,986,989} The diagnostic rate for coronary artery lesions is similar to that of radionuclide imaging. Although the equipment is simpler and less expensive than for other methods,\textsuperscript{9} interobserver variability is large and a highly skilled operator is required. Use of transverse contrast to enhance the visibility of wall motion, application of 3-dimensional echocardiography to simplify image acquisition, and application of tissue Doppler and tissue tracking methods to objectively evaluate wall motion are expected in the future.\textsuperscript{984}

\section*{ii) Evaluation of Coronary Flow Velocity}

Advances in Doppler ultrasonography have enabled direct visualization of coronary flow velocity signals, allowing noninvasive diagnosis of coronary artery lesions based on evaluation of CFR and visualization of stenotic blood flow.\textsuperscript{134} Coronary flow velocity signals are visualized by the color Doppler method, and coronary flow profile is recorded by the pulsed Doppler method.\textsuperscript{2} The detection rate of blood flow in the left anterior descending artery is as high as 90\%, but the detection rate of the right coronary artery and left circumflex artery is slightly lower.\textsuperscript{984} In patients with coronary artery stenosis, the normal diastolic dominance of flow velocity is lost, and a characteristic waveform is noted, with slow blood flow persisting throughout the cardiac cycle. Measurement of CFR with ATP or dipyridamole stress loading has been found to be useful for the diagnosis of mild lesions causing \textasciitilde{}50\% coronary artery stenosis. It is not only useful for detecting coronary artery lesions, but also for identifying myocardial microvascular obstruction.\textsuperscript{134,990,991} For evaluation of coronary artery lesions by echocardiography, refer to the individual methods in this Guideline.

\section*{d. Cardiac Radionuclide Imaging}

Cardiac radionuclide imaging allows noninvasive, physiological imaging, and stress and rest myocardial perfusion SPECT are widely used for the diagnosis of coronary heart disease in daily clinical practice. If exercise stress loading is impossible or contraindicated, myocardial ischemia can still be diagnosed by using vasodilators.\textsuperscript{2} Regarding the diagnostic accuracy of exercise myocardial perfusion SPECT for coronary artery stenosis (\textasciitilde{}50\%), a sensitivity of 96\% and a specificity of 36–96\% have been reported. With adenosine stress loading, the sensitivity and specificity were 75–96\% and 38–100\%, respectively.\textsuperscript{207} In the past, diagnostic accuracy was studied by comparison with morphological stenosis on coronary angiography. However, the diagnostic accuracy of myocardial perfusion SPECT has more recently been compared with that of FFR (\textasciitilde{}0.8), which is a method used for evaluation of functional coronary artery stenosis.\textsuperscript{202}

Because myocardial perfusion SPECT shows the relative blood flow distribution, there used to be a potential problem of false-negative results in patients with balanced ischemia due to triple-vessel disease or left main trunk disease.\textsuperscript{218,266} However, development of a semiconductor gamma camera dedicated to the heart has made quantitative evaluation of myocardial blood flow possible,\textsuperscript{267,268} and good diagnostic accuracy has been achieved for triple-vessel disease and left main trunk lesions, with a sensitivity of 86\%, specificity of 78\%, and accuracy of 80\%.\textsuperscript{269}

Quantitative measurement of ischemic myocardium is possible using stress myocardial blood flow SPECT. Coronary revascularization improves the prognosis compared with pharmacotherapy and the incidence of cardiac events increases as the amount of ischemic myocardium increases in the case of ischemic myocardium accounting for more than 10\% of the total left ventricular myocardium.\textsuperscript{227,300} Therefore, when determining the indications for coronary revascularization, it is recommended to confirm whether ischemic myocardium accounts for 10\% or more of the total left ventricular myocardium by performing stress myocardial perfusion SPECT, etc.\textsuperscript{127} For assessment of coronary artery lesions by radionuclide imaging, see the sections on each test in this Guideline.

\section*{2.1.3 Invasive Evaluation}

Although noninvasive modalities such as MDCT have become available for assessing coronary artery stenosis, coronary angiography remains the gold standard. Conventionally, in addition to the criterion that 75\% should be the threshold for significant stenosis as in the AHA classification, quantitative measurements can be carried out, such as edge detection and video densitometry.\textsuperscript{442} Quantitative assessment is essential to monitor changes over time in the same patient, such as assessing a lesion before and after PCI or the response to drug therapy in an interventional study.\textsuperscript{992}

Findings obtained by IVUS have shown that coronary angiography alone cannot adequately assess the clinical significance of coronary artery stenosis.\textsuperscript{993,994} Because coronary angiography provides a projection of the vessel lumen, the characteristics of the vessel wall and the extent of vascular remodeling cannot be assessed. If a lesion only causes moderate stenosis, the presence or absence of ischemia is a key point.\textsuperscript{730} In such cases, functional evaluation using a pressure guidewire\textsuperscript{568} or Doppler guidewire\textsuperscript{264} is useful, in addition to morphological assessment by IVUS, angioscopy, etc. Obtaining the FFR at the time of coronary angiography to assess the functional severity of coronary artery stenosis can help to determine whether a lesion is causing myocardial ischemia and to make decisions about treatment strategies.\textsuperscript{999} Care should be exercised in patients who have microvascular obstruction, such as those with myocardial hypertrophy or diabetes mellitus, as CFR will
decrease even in the absence of coronary artery stenosis.

2.2 Coronary Artery Lesion Assessment in Myocardial Infarction

2.2.1 Targets for Evaluation

When evaluating coronary artery stenosis in patients with myocardial infarction, the presence/absence of residual myocardium in the infarct zone, the presence/absence of ischemia in the noninfarct zone, and left heart function are also important factors to consider. If angina symptoms are present, the extent of coronary artery stenosis should be examined in the infarcted and noninfarcted regions of the myocardium. Determining the presence/absence of objective ischemic findings is important in patients with myocardial infarction, because asymptomatic ischemia is common. In patients with poor left ventricular function (LVEF <40%), assessing the extent of coronary artery stenosis is essential to predict the prognosis.

2.2.2 Evaluating the Extent of Stenosis

Evaluation of coronary artery lesions in the noninfarcted areas is performed similarly to evaluation of lesions in patients with stable coronary heart disease. With regard to evaluation of ischemia in the infarct zone, microvascular obstruction in the myocardium modifies the CFR, raising the possibility that functional evaluation may not correctly assess the extent of stenosis. Therefore, assessment of coronary artery stenosis is performed by morphological assessment. MDCT is used for noninvasive testing.

In Japan, revascularization by PCI is frequently performed in patients with myocardial infarction, and MRA, which cannot examine the stent lumen, is not appropriate for evaluating the culprit coronary artery. Invasive evaluation methods include coronary angiography, IVUS, angioscopy, and OCT. Particularly, IVUS and OCT have additional value for detecting plaque rupture at the culprit lesion, and angioscopy can diagnose unstable lesions by observing yellow plaques or thrombi.

2.2.3 Postinfarction Angina and Asymptomatic Myocardial Ischemia

Postinfarction angina is angina that occurs following myocardial infarction. Its incidence is 20% in patients receiving thrombolytic therapy alone and 6% in those treated by PCI and the incidence is even lower with PCI or percutaneous coronary stenting for stable coronary heart disease. That is, a clear medical rationale is required to perform PCI and stenting. Specifically, unidirectional imaging of >75% stenosis is sufficient for ACS (acute myocardial infarction and unstable angina), but the following requirements need to be satisfied for stable coronary heart disease: (1) >90% stenosis, (2) a stenotic lesion that is thought to cause stable effort angina (only in the absence of other significant lesions), and (3) additional diagnostic testing for functional ischemia that identifies the stenotic lesion as the cause of functional ischemia. This suggests that the need for noninvasive tests such as CCTA, cardiac MRI, echocardiography, and radionuclide imaging is likely to increase in the future, as well as Doppler and pressure guidewire testing to assess functional myocardial ischemia. On the other hand, invasive assessment is essential for selecting the devices for PCI and deciding treatment endpoints.

2.3 Assessment of Myocardial Ischemia and Lesions Associated With PCI

Assessment of myocardial ischemia and coronary artery lesions is essential to determine the indications for PCI. According to a new requirement in the 2018 revision of the 2018 Malaysian Cardiological Society (MCS) guidelines, functional assessment of ischemia in the infarct zone, microvascular obstruction, and myocardial viability, which can be assessed by contrast-enhanced MDCT as well. In the future, noninvasive tests such as MDCT will become important in addition to use of intravascular imaging to identify “vulnerable patients,” so that ACS can be prevented in patients with chronic coronary heart disease.

2.3.1 Selection of Devices

Quantitative measurement of vessel diameter by coronary angiography or intracoronary imaging is essential to determine the size of the balloon or stent for PCI. Use of IVUS or OCT not only allows evaluation of the extent of luminal stenosis, but also observation of the vessel walls and plaque characteristics, such as calcification, that are not evident on coronary angiography.

2.3.2 Deciding the Endpoints

A recent comparison of coronary angiography-guided and IVUS-guided PCI showed that better outcomes were obtained by angiography-guided PCI. Predictors of stent thrombosis or restenosis after stenting include poor stent expansion, residual disease, thrombus, and coronary artery dissection. The minimum stent area is also a predictor of in-stent restenosis, and IVUS observation can provide useful information for determining PCI endpoints.

2.3.3 Post-Treatment Evaluation and Follow-up

There is some risk of restenosis after PCI, however it is performed. The incidence of restenosis is 5–10% when DES are used, which is significantly lower than with conventional stents (bare metal stents). In Japan, coronary angiography is sometimes performed 6 months after PCI to check for restenosis. However, the recent ReACT study performed in Japan found no clinical benefit of follow-up.
coronary angiography at 8–12 months after PCI, and there was a higher incidence of target lesion revascularization within 1 year in the follow-up angiography group.\textsuperscript{4,7}

Post-treatment assessment and follow-up using noninvasive techniques such as MDCT and cardiac MRI would be meaningful if it could be achieved. With MDCT, it is possible to identify changes in coronary artery lesions, including plaque progression and regression, and detect noncalcified vulnerable plaques, as well as the changes in treated lesions. Assessment of the stent lumen by MDCT has already been successful for stents of \( \geq 3 \) mm placed at a proximal site. Coronary MRA cannot visualize the stent lumen, but the presence/absence of myocardial ischemia on stress myocardial perfusion MRI may allow the diagnosis of restenosis.\textsuperscript{2}

### 3. Diagnosis of Myocardial Viability

Myocardial viability indicates myocardial characteristics by which contractility is preserved or impaired by myocardial infarction or severe ischemia. However, contractility may be improved by appropriate revascularization therapy for the ischemic region.\textsuperscript{1023} This concept was derived from the observation that revascularization for coronary heart disease, mainly by PCI and CABG procedures, often improves the function of myocardial regions with reduced contractility and that regions responding to positive inotropic stimulation responded to revascularization. Thus, the concept of myocardial viability is clinically oriented, but requires assessment of blood flow and metabolism, as well as global and regional left ventricular function. If viable myocardium is present near the endocardium, myocardial contractility may be restored by alleviating ischemia, even in patients with myocardial infarction. Therefore, accurate diagnosis of viable myocardium is essential when determining the indications for PCI and CABG. When myocardial perfusion SPECT imaging and dobutamine stress transthoracic echocardiography (TTE) are performed, greater recovery of left ventricular function is associated with a more favorable prognosis,\textsuperscript{229,1024} and this is highly useful for predicting the patient’s prognosis. Myocardial viability covers 2 conditions: hibernating and stunned myocardium. Hibernating myocardium is viable myocardium that is affected by severe ischemia from severe coronary stenosis and has lost its contractility.\textsuperscript{154} Hibernating myocardium may persist for several months, similar to an animal that is hibernating and waiting for spring. In this condition, myocardial contractility can be improved by revascularization of the ischemic region or by reducing myocardial oxygen demand.\textsuperscript{1021} It is thought that regional metabolism decreases to prevent myocardial necrosis by reducing energy consumption, and revascularization is an effective treatment for myocardium in this state.

Stunned myocardium is myocardium that has been exposed to severe ischemia and shows persistent loss of left ventricular contractility even after ischemia resolves.\textsuperscript{1025} Stunned myocardium was first discovered in an animal study when the recovery of left ventricular wall motion was delayed after resolution of transient ischemia caused by coronary ligation. Clinically, stunned myocardium is observed after revascularization is performed for effort angina, vasospastic angina, or myocardial infarction. Stunned myocardium can be likened to animals that remain stunned for a certain period after a crisis. Impairment of cardiac contraction due to stunned myocardium usually resolves within a few hours. However, in chronic myocardial stunning, the stunned myocardium may persist for weeks after revascularization for myocardial infarction. Because blood flow has already been restored to the sites of stunned myocardium, diagnosis requires confirmation of the presence of blood flow by coronary angiography or radionuclide imaging.

Recently, it was reported that resting blood flow and oxygen metabolism are relatively maintained in some areas

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**Table 51. Recommendations and Levels of Evidence for Testing Methods to Assess Coronary Artery Lesions**

<table>
<thead>
<tr>
<th>Test Method</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
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<tr>
<td>Coronary angiography</td>
<td></td>
<td></td>
<td>V</td>
<td>V</td>
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<tr>
<td>Anatomical assessment</td>
<td>I</td>
<td>C</td>
<td>B</td>
<td>V</td>
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<tr>
<td>Assessment of stenotic lesions</td>
<td>I</td>
<td>B</td>
<td>A</td>
<td>III</td>
</tr>
<tr>
<td>Assessment of vulnerable plaque</td>
<td>Iib</td>
<td>C</td>
<td>C1</td>
<td>IVb</td>
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<td>CCTA</td>
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<tr>
<td>Anatomical assessment</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>IVb</td>
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<tr>
<td>Assessment of stenotic lesions</td>
<td>Iib</td>
<td>B</td>
<td>B</td>
<td>II</td>
</tr>
<tr>
<td>Assessment of vulnerable plaque</td>
<td>Iib</td>
<td>C</td>
<td>C1</td>
<td>IVb</td>
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<td>Cardiac MRI</td>
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<tr>
<td>Anatomical assessment</td>
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<td>Assessment of stenotic lesions</td>
<td>Iib</td>
<td>B</td>
<td>B</td>
<td>II</td>
</tr>
<tr>
<td>Assessment of vulnerable plaque</td>
<td>Iib</td>
<td>C</td>
<td>C1</td>
<td>IVb</td>
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<tr>
<td>Echocardiography</td>
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<tr>
<td>Assessment of stenotic lesions</td>
<td>Iib</td>
<td>C</td>
<td>C1</td>
<td>IVb</td>
</tr>
<tr>
<td>Assessment of vulnerable plaque</td>
<td>Iib</td>
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<td>C1</td>
<td>IVb</td>
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<tr>
<td>Cardiac radionuclide imaging</td>
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<tr>
<td>Assessment of stenotic lesions</td>
<td>Iib</td>
<td>C</td>
<td>C1</td>
<td>II</td>
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<tr>
<td>IVUS/OCT</td>
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<tr>
<td>Assessment of stenotic lesions</td>
<td>Iib</td>
<td>B</td>
<td>B</td>
<td>III</td>
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<tr>
<td>Assessment of vulnerable plaque</td>
<td>Iib</td>
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<td>Angioscopy</td>
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<td>Assessment of stenotic lesions</td>
<td>Iib</td>
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<td>C1</td>
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<tr>
<td>Assessment of vulnerable plaque</td>
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<td>C1</td>
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<tr>
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<tr>
<td>Assessment of stenotic lesions</td>
<td>Iib</td>
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<td>IVb</td>
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<tr>
<td>Intracoronary pressure measurement</td>
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<tr>
<td>Assessment of stenotic lesions</td>
<td>I</td>
<td>A</td>
<td>A</td>
<td>I</td>
</tr>
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</table>

CCTA: coronary computed tomography angiography; COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.
of hibernating myocardium; therefore, some cases cannot be explained by the theory outlined above. Another hypothesis of hibernating myocardium is that repeated intermittent myocardial stunning causes hibernation, because the perfusion reserve is reduced in hibernating myocardium.\textsuperscript{1025-1027} It is also unclear whether stunned and hibernating myocardium are sequential or occur independently of each other. Pathologically, the sarcolemma is decreased in hibernating myocardium, but the cell volume of the cardiomyocytes is not decreased. Restoration of contractility is associated with de-differentiation, but if there are advanced pathological changes, the extent of recovery and prognosis are poor. Whether it is hibernating myocardium or stunned myocardium, detection of viable myocardium is very important both scientifically and clinically. However, currently, there is no generally accepted definition of myocardial viability. In addition, it is important to noninvasively assess the 3-dimensional anatomy of the LV with good spatial and temporal resolution, as well as accurate evaluation of blood flow, metabolism, cardiomyocyte membrane function, and left ventricular systolic and diastolic function. Recommendations and levels of evidence for assessing coronary lesions are shown in Table S5.

\textbf{3.1 Detection Using Various Diagnostic Modalities}

\textbf{3.1.1 ECG}

Assessment of myocardial viability by ECG is based on the presence of abnormal Q waves, ST elevation, exercise ECG findings, and QT dispersion. The presence of abnormal Q waves reflects transmural necrosis of the myocardium just below the lead site, and the extent of necrotic myocardium can be estimated from the number of leads with abnormal Q waves. However, there can be some viable areas in the estimated infarcted myocardium of patients with Q-wave myocardial infarction.

In patients with myocardial infarction, ST elevation occurs frequently in leads over the infarct zone during exercise. This underlying mechanism may include ischemia of the residual viable myocardium in the infarct zone or reciprocal changes in the contralateral myocardium. However, exercise-induced deterioration of left ventricular wall motion may also cause such a phenomenon; therefore, the occurrence of ST elevation does not always suggest the presence of ischemia or indicate myocardial viability. A study evaluating the mechanism of exercise-induced ST elevation by comparison with F-18 FDG PET\textsuperscript{35} revealed that ST elevation showed a sensitivity of 66\% and a specificity of 100\% for the diagnosis of myocardial viability, and ST elevation in the infarct zone during dobutamine challenge had a sensitivity of 69\% and a specificity of 83\% for the diagnosis of myocardial viability.\textsuperscript{1028} Thus, specificity was good in both cases, but sensitivity was not excellent. In patients with single-vessel disease and myocardial infarction, ST depression in the noninfarct zone during exercise corresponded to myocardial viability on F-18 FDG-PET performed in 44 patients with previous myocardial infarction,\textsuperscript{1031} a QT dispersion $\geq$70 ms showed a sensitivity and specificity for myocardial viability of 83\% and 71\%, respectively.

As described above, assessment of myocardial viability by ECG has several limitations, and it should only be used as necessary in the case of other tests not being able to be performed.

\textbf{3.1.2 Transthoracic Echocardiography (TTE)}

Resting TTE is widely used for the diagnosis and evaluation of chronic coronary heart disease because it is noninvasive, convenient, and has rapid image acquisition. However, its diagnostic performance depends highly on the quality of the images obtained. Moreover, resting TTE only provides semiquantitative evaluation and the quality of the images obtained and the results are influenced by the skill and experience of the operator. The detection of myocardial viability using TTE is based mainly on the contractile reserve in loading tests, and assessment has been carried out using contrast medium in recent years.

\textbf{a. Evaluation of LV Morphology}

In patients with previous myocardial infarction, the presence of mural thinning, increased echogenicity in the left ventricular (LV) myocardium, and LV aneurysm formation are indicators of the presence of severe LV myocardial fibrosis, and myocardial viability can be poor at sites showing such changes. If the LV wall does not show thinning in the chronic phase of infarction, there may be a possibility of hibernating or stunned myocardium, even in the absence of LV wall motion.

\textbf{b. Evaluation of LV Wall Motion and Dobutamine Stress Test}

Tracing the movement of the LV endocardium is used as the basis for evaluating LV wall motion by TTE, with contour extraction being carried out manually or automatically using B-mode images. LV wall motion is assessed by the centerline method to avoid the effects of anteroposterior cardiac movement. Both the movement of the endocardium and the increment in LV wall thickness during systole are evaluated.

The presence of LV wall motion in the resting state is evidence of myocardial viability, but it is difficult to distinguish between hibernating or stunned myocardium by resting TTE alone if the LV wall motion is severely impaired. Therefore, a pharmacological stress test should be performed to see whether wall motion is altered. Among the various tests, dobutamine loading is the most popular. A coronary artery occlusion/reperfusion study showed that intravenous infusion of dobutamine at a rate of 100\% of the resting myocardial viability by stress TTE, several observational studies have shown that patients with detectable myocardial viability may have an improved prognosis after revascularization.\textsuperscript{1033,1034} Impaired LV wall motion after thrombolytic therapy for acute myocardial infarction, which indicates myocardial stunning, is improved by dobutamine administration.\textsuperscript{1035}
It has also been shown that restoration of LV wall motion after revascularization can be predicted by improvement of impaired LV wall motion, an indication of hibernating myocardium, during dobutamine stress TTE in patients with multivessel disease. Charney et al compared dobutamine stress TTE with resting thallium-201 (TI-201) cardiac perfusion SPECT and showed that the ability to predict myocardial viability after revascularization was similar but TTE was less expensive than resting TI-201 SPECT. When low-dose dobutamine stress TTE is performed to assess myocardial viability, the infusion of dobutamine is usually started at 2 μg/kg/min and blood pressure is measured every minute together with monitoring of the ECG. If there are no symptoms, ST changes on the ECG, frequent occurrence of arrhythmias, marked elevation of blood pressure (≥200 mmHg), or a decrease in systolic blood pressure by ≥20 mmHg, the infusion rate is increased by 2 μg/kg/min every 3 min up to 10 μg/kg/min.

The LV long-axis, short-axis, apical 2-chamber, and 4-chamber images are recorded before dobutamine loading and during each loading stage, and then the TTE images obtained before and after loading are displayed simultaneously for visual judgment of LV wall motion. Viable myocardium can be present when LV wall motion is improved in akinetic or severely hypokinetic regions. The sensitivity and specificity of low-dose dobutamine stress TTE for detecting viable myocardium is reported to be 80–90%, 1,103,1036,1038,1042. The most common adverse reaction to dobutamine is induction of arrhythmia, generally premature supraventricular or ventricular contractions. If supraventricular or ventricular tachycardia occurs, testing should be discontinued. If anginal pain occurs, the test should also be discontinued and nitroglycerin should be given immediately either sublingually or as a spray. As with other stress tests, emergency drugs and a cardiac defibrillator should be available. Contraindications to dobutamine stress testing are similar to those for other stress tests and generally include (1) acute myocardial infarction (4–10 days previously), (2) unstable angina, (3) known left main trunk artery stenosis, (4) obvious congestive heart failure, (5) severe, life-threatening tachyarrhythmia, (6) severe valvular stenosis, (7) hypertrophic obstructive cardiomyopathy, (8) acute pericarditis/myocarditis and endocarditis, and (9) aortic dissection (Table 52). 1,1043 Direct observation is the usual method of detecting abnormal LV wall motion.

However, for detecting viable myocardium, strain imaging, which is a new method for accurate assessment of regional myocardial motion, has been reported in recent years, 1,1044,1045 and concomitant use of strain imaging with direct LV wall motion observation may improve sensitivity. The disadvantages of using stress TTE for the evaluation of myocardial viability include poor delineation, qualitative judgment, and low inter-rater reproducibility. However, it was reported that use of the tissue Doppler method 1,1046 to detect myocardial contraction in combination with dobutamine stress TTE improved the accuracy of assessing myocardial viability and exercise tolerance. 1,1047 Other stress loading modalities include exercise, dipyridamole, 1,1035 adenosine triphosphate, and nitroglycerin, but their usefulness is less clear compared with dobutamine stress TTE.

### c. Myocardial Contrast TTE

When selective coronary arteriography is performed, myocardial contrast TTE is being used more frequently to evaluate peripheral run-off after intracoronary injection of a contrast agent for judgment of myocardial viability. Theoretically, myocardial contrast TTE is useful for the evaluation of myocardial stunning in patients with acute myocardial infarction undergoing revascularization. Unlike the determination of contractile reserve by dobutamine stress TTE, myocardial contrast TTE is not affected by factors such as residual coronary artery stenosis, coronary reserve, myocardial necrosis, or interstitial fibrosis. According to a cohort study, myocardial contrast TTE showed lower specificity compared with TI scintigraphy for detecting viable myocardium related to restoration of cardiac function, but its sensitivity was comparable. 1,1048 The combination of myocardial contrast TTE and dobutamine stress TTE is expected to improve sensitivity in the future. However, the use of current contrast agents for the heart is not covered by health insurance at present.

Even when revascularization is successful, poor inflow of contrast medium into the infarcted myocardium may occur, 1,198,1049 that is, the “no-reflow” phenomenon, which is considered to indicate microvascular obstruction due to reperfusion injury. Myocardium exhibiting the no-reflow phenomenon shows delayed recovery of wall motion after revascularization, and abnormal LV wall motion often persists. Various intravenous contrast media have been developed recently, leading to the possibility of evaluating myocardial viability by injecting contrast medium into a peripheral vein. Although previous transvenous myocardial contrast TTE techniques only achieved poor image quality, the development of echo contrast agents and advances in ultrasound devices have improved image quality. Wide clinical application has been promoted by use of various noise reduction methods based on second harmonic imaging and intermittent transmission to minimize the destruction of microbubbles by ultrasonic waves. There is no contrast staining of nonviable tissues where the culprit coronary artery is completely occluded and the myocardium is largely fibrotic.

#### 3.1.3 Cardiac Radionuclide Imaging

With regard to assessment of myocardial viability by radionuclide imaging, TI-201, technetium-99m (Tc-99m), I-123-BMIPP, and I-123-meta-iodobenzyl-guanidine (MIBG) are used for SPECT, with 18F-FDG and nitrogen-13 ammonia being used for PET in the clinical setting. PET

<table>
<thead>
<tr>
<th>Table 52. Contraindications for Dobutamine Stress Echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction (within 4–10 days after onset)</td>
</tr>
<tr>
<td>Unstable angina</td>
</tr>
<tr>
<td>Patients with documented left main trunk artery stenosis</td>
</tr>
<tr>
<td>Obvious congestive heart failure</td>
</tr>
<tr>
<td>Severe, life-threatening tachyarrhythmia</td>
</tr>
<tr>
<td>Severe valvular stenosis</td>
</tr>
<tr>
<td>Hypertrophic obstructive cardiomyopathy</td>
</tr>
<tr>
<td>Acute pericarditis/myocarditis and endocarditis</td>
</tr>
<tr>
<td>Aortic dissection</td>
</tr>
</tbody>
</table>

(Reproduced from Krahvinkl et al 1997,1,1043 with permission from Oxford University Press on behalf of the European Society of Cardiology. OUP and the ESC are not responsible or in any way liable for the accuracy of the translation. The Japanese Circulation Society is solely responsible for the translation in this publication/reprint.)
tracers, such as oxygen-15-labeled water and rubidium-82, are not yet covered by health insurance, but are expected to be used in the future.

a. TI-201
Myocardial perfusion imaging is the main cardiac radionuclide imaging modality and is used to diagnose and assess coronary heart disease. TI-201 is an analog of potassium that is actively taken up by cardiomyocytes via Na/K ATPase, allowing assessment of myocardial viability based on membrane integrity. After being injected intravenously, TI-201 is distributed in proportion to myocardial blood flow and is taken up by cardiomyocytes. Regions of ischemia and infarcts are depicted as reduced TI-201 accumulation. TI-201 redistribution occurs because when blood flow is decreased in ischemic myocardium, washout is slower than in normal myocardium or infarcted myocardium and the region of reduced accumulation in the early image appeared to improve the accumulation in the delayed image (obtained after 3–4 hours).

The differentiation of ischemic myocardium and infarcted myocardium is based routinely on the presence of redistribution. However, 30–50% of the myocardial areas without redistribution of TI-201 still show restoration of cardiac function after revascularization, and poor sensitivity is a problem when predicting recovery of LV systolic function based on redistribution. To improve sensitivity, redistribution is assessed at 24 hours or in the resting state, or an additional dose of TI-201 is administered (reinjection method) after late exercise imaging. According to a review by Bax et al, although TI-201 shows good sensitivity for the assessment of viability, it has lower specificity compared with TTE. Attempts have been made to improve accuracy by adding information on cardiac function and by correction of SPECT attenuation. Innovations in imaging equipment have enabled fusion images with CT to be obtained, and application to correction of attenuation is expected in the future.

b. Tc-99m-Labeled Myocardial Perfusion Agents
Using Tc-99m-labeled myocardial perfusion agents such as Tc-99m MIBI and Tc-99m tetrofosmin, myocardial viability can be assessed from accumulation, as with TI-201. These agents have been reported to achieve detectability comparable to that of TI-201. In most studies, viable myocardium was defined as areas where Tc-99m-labeled myocardial perfusion agents showed at least 50–60% accumulation relative to normal myocardium, and this definition is widely accepted.

With Tc-99m-labeled myocardial perfusion agents, indices of LV function can be calculated easily by the first-pass technique or by ECG-gated myocardial perfusion SPECT. Therefore, the accuracy of assessing myocardial viability can be improved by considering information such as LV wall motion and changes in wall thickness in addition to myocardial blood flow. These methods are useful for predicting cardiac function after revascularization. These methods are useful for predicting cardiac function after revascularization. A Japanese prospective multicenter observational study of resting ECG-gated Tc-99m-MIBI SPECT also showed good reproducibility of both functional information and myocardial accumulation, and combining such information was found to be useful for predicting the improvement of LV wall motion after revascularization. Dobutamine stress ECG-gated myocardial perfusion SPECT is also useful for the diagnosis of myocardial viability based on cardiac functional reserve.

Because retention of Tc-99m MIBI is associated with decreased mitochondrial function, attention has been paid to the relationships among Tc-99m MIBI washout and cardiac function, myocardial viability, and the prognosis in patients with heart failure and triple-vessel disease. A clinical investigation has already been reported, and future application is expected.

Tsai et al performed a meta-analysis of 8 studies comparing Tc-99m MIBI and Tc-99m tetrofosmin SPECT with PET as the gold standard for assessment of myocardial viability in patients with coronary heart disease. Under these conditions, they demonstrated an integrated sensitivity and specificity of 82% (95% CI: 81–84) and 88% (95% CI: 86–90), respectively, indicating that SPECT shows good detectability.

c. Assessment of Metabolism Using PET
The main energy sources for the myocardium are free fatty acids and glucose. In the fasting state, healthy myocardium obtains more than 60% of its energy from fatty acids, whereas ischemic myocardium depends on utilizing glucose by glycolysis. As ischemia progresses, anaerobic glycolysis becomes predominant, and further progression leads to myocardial necrosis with loss of metabolism. Hence, it is possible to examine the presence and extent of myocardial ischemia in detail by measuring the local utilization of energy substrates in the myocardium. Blood flow data and the accumulation of 18F-FDG, which indicates glucose metabolism, can be obtained by PET. Regions of enhanced glucose metabolism associated with reduced myocardial function and blood flow represent hibernating myocardium, whereas low with poor function and blood flow represent infarcted myocardium. This method can predict, with 80–90% accuracy, which areas of myocardium showing impaired function will recover after revascularization.

Furthermore, a meta-analysis showed that patients with myocardial regions showing increased glucose metabolism associated with reduced function and blood flow are more likely to develop cardiac events, and thus require revascularization. FDG-PET has a sensitivity of 88% and specificity of 73% according to a report on the prediction of restoration of cardiac function, indicating superior specificity over the evaluation of blood flow. Thus, FDG-PET has long been the gold standard for detecting viable and salvageable myocardium. A comparison with other diagnostic modalities by Bax et al showed that FDG-PET is the most sensitive modality for predicting recovery of LV wall motion, but dobutamine stress TTE had the highest specificity. According to a meta-analysis of 9 studies (target LVEF <40%) that combined clinical data, FDG-PET had a sensitivity of 91% (80–100%) and a specificity of 61% (44–92%) for predicting functional recovery in regions of LV scar tissue and hibernating myocardium detected by PET. Thus, the sensitivity of FDG-PET is higher than that of other diagnostic modalities, and it is the best option for assessment of myocardial viability, especially in patients with LV dysfunction for whom revascularization is being considered.

On the other hand, a meta-analysis of studies in which revascularization was performed based on the assessment of viability by FDG-PET showed that revascularization significantly improved the prognosis, but there was no difference between FDG-PET and stress TTE or SPECT.
However, it is often impossible to obtain adequate images by other methods in patients with severe coronary heart disease, whereas PET can provide clear images and has an important role in such cases. The use of dobutamine challenge with FDG-PET has also been attempted.  

FDG-PET has been covered by Japanese health insurance since 2002, and a domestic system for the supply of ¹⁸F-FDG is being established, making it possible to image glucose metabolism by installing a PET camera without a cyclotron. In addition, imaging of glucose metabolism is possible by attaching a special collimator or coincidence circuit to SPECT equipment. Although high-quality images like those provided by PET cannot be obtained with FDG SPECT, the evaluation of myocardial viability is comparable to that with PET.  

### 3.1.4 Cardiac MRI  
#### a. Methods  
Detection of myocardial viability by cardiac MRI can be divided into 2 categories: evaluation of cardiac morphology and wall motion with cine MRI, and diagnosis of fibrotic infarcts by LGE MRI.

#### i) Contractile Reserve  
Two cardiac MRI findings are used to detect hibernating myocardium in the absence of contraction in the resting state: the retention of absolute wall thickness and the restoration of wall motion after stress loading. The former is defined as an end-diastolic wall thickness ≥5.5 mm, and the latter is usually defined as an increment in systolic wall thickness by ≥2 mm compared with end-diastolic thickness during low-dose dobutamine loading. Either ECG-gated cine MRI or high-speed MRI can be used in this context. Dobutamine is administered by intravenous infusion at a rate of 10 µg/kg/min via a peripheral vein, and imaging is performed after 3–5 min. The tagging method may be used to evaluate LV wall motion during dobutamine challenge. The sensitivity and specificity of the cardiac MRI contractile reserve for detecting viable myocardium is 88% and 87%, respectively, compared with assessment of viability by PET at 89% and 94%, respectively, on the basis of improvement of cardiac function.  

Assessment of stunned myocardium is performed by a similar method. Low-dose dobutamine challenge has been reported to increase systolic wall thickness by ≥2 mm at sites of stunned myocardium and quantitative assessment of regional cardiac function by tagging has also been attempted. According to a joint statement on dobutamine stress cardiac MRI from various Canadian academic societies (CCS/CAR/CANM/CNCS/CanSCMR Joint Position Statement on Advanced Noninvasive Cardiac Imaging), a meta-analysis of 10 studies with a total of 401 cases showed that the sensitivity and specificity of dobutamine stress cardiac MRI were 94% and 94%, respectively, for detection of myocardium with restoration of contractility during follow-up after revascularization, a result that was equal or better than dobutamine stress TTE.  

#### ii) Detection of Myocardial Fibrosis by LGE on T1-Weighted MRI  
LGE on T1-weighted MR images obtained with gadolinium contrast medium is the gold standard for the detection of myocardial fibrosis and is used to assess myocardial viability. Compared with SPECT or PET, cardiac MRI has superior spatial resolution, and the assessment of LGE allows for clarification of the location and function of myocardial regions with scarring/fibrosis, as well as the extent of lesions, such as whether they are transmural or subendocardial. Thus, unrecoverable myocardium with scarring/fibrosis can be identified with high diagnostic accuracy. Although a very high diagnostic concordance rate with radionuclide imaging of myocardial viability has been
shown for transmural infarction, 47% of the affected regions could not be detected by radionuclide modalities such as SPECT at sites of subendocardial infarction where <50% of the wall thickness showed contrast enhancement on cardiac MRI. As described above, LGE MRI can clearly show areas of myocardial fibrosis among regions of hibernating or stunned myocardium, and it is very useful for assessing the disease state and for determining the appropriate treatment strategy such as revascularization.

b. Features and Advantages
An important advantage to using MRI for the detection of myocardial viability is that there is no radiation exposure, unlike radionuclide imaging or CT. Because of its excellent spatial resolution, cardiac MRI can easily distinguish the boundary between the endocardial and epicardial surfaces. It is also possible to obtain the desired cross-sectional images for each cardiac phase. Disadvantages of cardiac MRI include a longer acquisition time and the need for a technician who is skilled at imaging and knowledgeable about pathological conditions. Artifacts caused by the heart beating and by breathing are a problem, but can be improved by high-speed imaging. ECG gating, and respiration gating. With the use of contrast medium, changes in intramyocardial contrast enhancement over time can be measured quantitatively. It is safe to say that the assessment of myocardial viability with LGE MRI is established clinically.

c. Diagnostic Performance
Assessing myocardial viability using FDG-PET in patients with chronic myocardial infarction is the gold standard, but the sensitivity and specificity of cardiac MRI for the detection of hibernating myocardium is 72% and 89%, respectively, based on the assessment of LV wall thickness. Low-dose dobutamine stress cardiac MRI provides more detailed information on stunned and hibernating myocardium, and may be used to predict the recovery of LV function and future cardiac events. In particular, accuracy for estimating the likelihood of recovery can potentially be improved when assessing the viability of myocardial regions that show LGE of 25–50% of the wall thickness. When transesophageal echocardiography and MRI were compared for examination of myocardial viability based on wall motion under dobutamine stress, transesophageal echocardiography showed a sensitivity of 77% and a specificity of 94%, while cardiac MRI had a sensitivity of 94% and a specificity of 100%. With regard to the diagnosis of myocardial stunning in patients undergoing revascularization after acute myocardial infarction using cardiac MRI for assessment of wall thickness, it was reported that the sensitivity was 92% and the specificity was 56% for predicting recovery of wall motion after 4–6 months, and the sensitivity and specificity improved to 89% and 94%, respectively, when the appearance of abnormal wall motion under dobutamine stress was used as the benchmark.

According to a joint statement on dobutamine stress cardiac MRI from various Canadian academic societies (CCS/CAR/CANM/CNCS/CanSCMR Joint Position Statement on Advanced Noninvasive Cardiac Imaging), a meta-analysis of 13 studies with a total of 357 patients showed that LGE had a sensitivity of 81% and a specificity of 83% for predicting recovery of LV function, a result comparable to that for PET and superior to SPECT.

d. Indications and Contraindications
Cardiac MRI is indicated for many patients with coronary heart disease who have myocardium of unknown viability, especially when imaging of the LV wall motion is poor by TTE. Sharples et al. recommend the following algorithm for the assessment of myocardial viability: (1) if the initial 2-dimensional TTE provides inadequate images of all or part of the LV, MRI should be performed, with an additional low-dose dobutamine stress cardiac MRI (if necessary); and (2) if 2D TTE provides adequate images of the entire LV, dobutamine stress TTE is recommended without cardiac MRI. However, there is no evidence from randomized controlled trials to support this algorithm or its cost-effectiveness.

The contraindications of MRI include internal metal implants and claustrophobia. However, some of the newer pacemakers, cardiac resynchronization therapy pacemakers, ICDs, and ICDs with biventricular pacing (cardiac resynchronization therapy defibrillator) are conditionally compatible with cardiac MRI. Use of gadolinium contrast medium in patients with severe renal dysfunction is limited by the risk of nephrogenic systemic fibrosis. In principle, use of gadolinium contrast medium should be avoided in patients with endstage renal disease on long-term dialysis and nondialysis patients with acute renal failure or chronic renal failure and an eGFR <30 mL/min/1.73 m² (calculated from the serum creatinine level). In MRI laboratories, it may not be easy to perform monitoring and emergency procedures; therefore, it is not appropriate to use this imaging modality in patients with advanced heart failure or those in whom severe arrhythmia may be provoked by dobutamine stress.

e. New Technologies
Recently, in the cardiac MRI field, quantitative measurement of myocardial extracellular volume by T1 mapping has become an important topic. In cases of diffuse myocardial fibrosis, LGE MRI may have difficulty in differentiating myocardium with diffuse myocardial fibrosis from normal myocardium. Moreover, because LGE MRI is a qualitative method, it cannot be used to assess slight changes in myocardial properties. The T1 mapping method has recently been developed for assessing myocardial tissue properties based on cardiac MRI, and it has become available in the clinical setting. This modality allows quantitative assessment of myocardial fibrosis as extracellular volume in patients with “diseases that cause diffuse myocardial fibrosis”, such as hypertensive heart disease, aortic valve stenosis, etc., and it is also actively used to assess myocardial viability in patients with myocardial infarction.

3.1.5 CT
The trend towards the use of multi-array cardiac CT peaked with the development of 320-row CT, after which new types of CT scanners were developed, such as dual-source CT, dual-energy CT, photon-counting CT, and spectrum CT. Retrospective ECG gating allows measurement of LV wall thickness and assessment of LV wall motion, and new modalities for the assessment of the myocardium are emerging based on these technologies. In addition, myocardial fibrosis can be visualized with conventional MDCT, as with cardiac MRI, by using the appropriate
tube voltage and high tube current after injecting approximately 100 mL of iodinated contrast medium, and then creating images by iterative reconstruction.\textsuperscript{1096}

a. Methods and Diagnostic Performance
Although use of contrast medium is essential with CT, LV wall thickness can be measured and LV wall motion can be assessed by retrospective ECG-gated imaging. The spatial resolution is much better than with radionuclide imaging and MRI. When 4-dimensional LV wall motion analysis is performed, wall motion display is smoother with 20-frame imaging at 5% intervals of the cardiac cycle (20 equal parts) than with 10-frame imaging reconstruction from 10 images obtained by dividing 1 cardiac cycle (RR interval) into 10 equal parts.

However, the underlying temporal resolution remains the same for both methods, and is actually inferior to the temporal resolution of TTE or cardiac MRI. Despite this, a recent meta-analysis showed a strong correlation of cardiac mass measured by CT with cardiac MRI as a benchmark (correlation coefficients of 0.93, 0.95, 0.93, and 0.96, respectively).\textsuperscript{1097} Stress myocardial CT with pharmacological stress, for example, is a new imaging method that can obtain both anatomical information and physiological information such as data on myocardial perfusion.\textsuperscript{1098}

b. Advantages
Advantages of assessing myocardial viability by CT include: (1) ability to observe all areas of the heart compared with TTE, which has difficulty in observing the apex; (2) short acquisition time; (3) performing imaging in the acute phase without restriction because of internal metallic implants, unlike cardiac MRI; and (4) simultaneous evaluation of coronary artery stenosis and LV wall motion in a single examination. In patients with myocardial infarction, not only fibrosis, but also fatty degeneration\textsuperscript{1022} and calcification may occur in the infarcted myocardium. These changes can be detected from differences in CT attenuation on CT scans.

c. Disadvantages
The disadvantages of CT include the need to use iodinated contrast medium and exposure to radiation. Delayed-enhancement imaging is more difficult with CT than with cardiac MRI because CT provides inferior image quality due to its lower contrast resolution.

d. New Technologies
In general, imaging with a low tube voltage is desirable for CT to clearly delineate late enhancement, which suggests the presence of myocardial fibrosis. However, the radiation dose is often not sufficient even when the tube current is maximized, resulting in noisy images. The difference between first-generation and second-generation 320-row CT scanners is that the maximum tube current can be set higher for low-voltage imaging with the latter scanners, and a high-quality image with reduced noise can be obtained by iterative image reconstruction. When the ability of 16-row CT, first-generation 320-row CT (normal tube voltage), and second-generation 320-row CT (using a low tube voltage plus iterative image reconstruction) to detect myocardial fibrosis was evaluated by comparison with cardiac MRI, it was found that the second-generation 320-row CT had the highest diagnostic performance and showed improved site-specific sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy at 73%, 97%, 85%, 95%, and 93%, respectively.\textsuperscript{1096}

e. Indications
The 2010 Guideline for the Appropriate Use of Cardiac CT states that because radiation exposure and use of contrast medium are inherent disadvantages of CT, it is inappropriate as the first choice for follow-up of myocardial infarction and assessment of LV function in patients with heart failure.\textsuperscript{1084} Nevertheless, if adequate images cannot be obtained by TTE or cardiac MRI because of technical problems, CT is appropriate for follow-up of myocardial infarction or evaluation of LV function in heart failure patients. This is largely due to progress in CT scanners, such as improvement of temporal resolution by dual-source CT and the emergence of 320-row CT enabling clear cardiac imaging even in patients with arrhythmia, as well as advances in workstations and analytical software. In patients with new-onset heart failure, assessment of the coronary arteries by CT to estimate the etiology is divided into 6 categories depending on the risk of coronary heart disease and the LVEF. According to this classification, coronary artery evaluation by CT is only “appropriate” if the LVEF is decreased and the risk of coronary heart disease is low or moderate; otherwise the appropriateness of CT is “inconclusive.”

f. Other Applications
During evaluation of LV function, CT is useful for examining the LV apex, which is difficult to observe by TTE. Particularly, it is considered that the accuracy for detection of apical thrombus, which occurs frequently in patients with LV apical hypokinesia, is higher with CT than TTE. Although the increase in radiation exposure associated with retrospective ECG gating is a disadvantage of CT, it is possible to reduce radiation exposure by tube current dose modulation, which involves increasing the tube current from end-systole to end-diastole and decreasing the current during the other phases of the cardiac cycle. Although image quality is reduced for the phase with lower tube current, evaluation of wall motion is still possible. With regard to assessing LV function, not only the LVEF, but also regional LV wall motion can be determined, and the accuracy of evaluating myocardial viability can be improved by combined assessment of the extent of LV systolic thickening, the presence/absence of low CT values in the LV myocardium, and information on the coronary arteries. As noted above, additional late-phase imaging with prospective ECG gating can also detect areas of myocardial fibrosis and inflammation with minimal additional radiation exposure, but this requires injection of more than the usual 50 mL of contrast medium.

If the LV volume is measured at each phase of the cardiac cycle after dividing it into 20 parts, an LV volume curve can be drawn, and, theoretically, LV diastolic function can be determined from this LV volume curve. However, even dual-source CT, which has the best temporal resolution currently, only has a temporal resolution of about 75 ms and is inferior to TTE or invasive left ventriculography (LVG).

Therefore, volume measurement is unreliable, especially in the fast-moving phases of the cardiac cycle, and the LV volume curve obtained by CT is considered to differ from the true volume curve, making it difficult to assess LV
diastolic function at present. As a potential new development for the evaluation of myocardial viability in the future, it may become possible to perform the same examinations as with cardiac MRI, such as assessment of myocardial extra cellular volume in patients with heart failure, by using spectrum CT to measure the myocardial iodine content.

### 3.1.6 Cardiac Catheterization and Invasive LVG

#### a. Methods

In patients with coronary heart disease undergoing cardiac catheterization, myocardial viability is assessed by invasive LVG. Transarterial invasive LVG is performed and moving images of the heart are recorded. Information on LV volume, LVEF, and regional LV wall motion is also obtained.

#### b. Interpretation of the Findings and Relationship With Disease

Regional wall motion on invasive LVG reflects myocardial contractility, and wall motion is visually assessed according to the AHA classification as normokinesis, hypokinesis, akinesis, or dyskinesis. As a method for quantitatively evaluating LV wall motion abnormalities, the centerline method is used widely and provides excellent quantitative data. Preservation of wall motion on invasive LVG is proof of myocardial viability. However, it is difficult to judge myocardial viability in patients with severely abnormal LV wall motion associated with myocardial stunning after prolonged ischemia or hibernating myocardium due to chronic ischemia.

Regardless, areas where LV wall motion improves due to PESP are considered to be viable. It should be noted that the absence of PESP does not always indicate lack of viability, and that improvement of LV wall motion due to PESP varies with the cardiac load. When determining myocardial viability from the improvement in LV wall motion with nitrate administration, the same caution is required as for the evaluation of PESP. It is difficult to assess myocardial viability based on the severity of coronary artery stenosis and coronary blood flow. The extent of collateral flow on coronary angiography often influences LV viability.

c. Features, Advantages, and Disadvantages

The greatest advantages of invasive LVG are that, different from TTE, it provides high-resolution images in all patients and the orientation of observation is constant. However, evaluation may be difficult due to inadequate imaging or arrhythmia. The disadvantages are that it is an invasive test and observation of LV wall motion under different loading conditions requires multiple imaging sessions unless biplane equipment for simultaneous imaging from 2 directions is used.

d. Indications and Contraindications

Invasive LVG is indicated for patients with suspected coronary heart disease. However, given the potential complications owing to its invasive nature, it is only indicated when the benefits of the information that can be obtained clearly outweigh the potential risks. TTE is preferred for the evaluation of LV wall motion before and after stress loading.

### 3.2 Criteria for Selecting Tests

One of the most significant reasons for assessing myocardial viability is to predict the outcome of revascularization in patients with myocardial infarction. In patients with old myocardial infarction, a variety of imaging modalities are used to assess myocardial viability before deciding on the indication for revascularization. Even in patients with reduced regional LV wall motion, viable hibernating myocardium may still exist, and therefore it is necessary to assess viability by performing stress TTE with low-dose dobutamine or myocardial blood flow imaging with exercise or pharmacological stress. At facilities with PET equipment, FDG-PET can be used as the gold standard.

Assessment of viability based on late enhancement and evaluation of LV wall motion has been applied clinically using cardiac MRI and CT in recent years. The absence of LV wall motion after severe transient myocardial ischemia, especially after revascularization, should be examined, because of the potential presence of viable stunned myocardium, and myocardial contrast TTE is also useful in such cases.

Observational studies have suggested that revasculariza-

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**Table 53. Meta-Analyses Assessing Detectability (%) of Hibernating Myocardium**

<table>
<thead>
<tr>
<th>No. of studies in each meta-analysis</th>
<th>Total no. of patients</th>
<th>Diagnostic test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>41 studies</td>
<td>1,421</td>
<td>Dobutamine stress echocardiography</td>
<td>82</td>
<td>80</td>
<td>77</td>
<td>85</td>
</tr>
<tr>
<td>40 studies</td>
<td>1,119</td>
<td>Ti-201 SPECT</td>
<td>87</td>
<td>55</td>
<td>64</td>
<td>81</td>
</tr>
<tr>
<td>25 studies</td>
<td>721</td>
<td>Tc-99m sestamibi SPECT</td>
<td>81</td>
<td>66</td>
<td>71</td>
<td>77</td>
</tr>
<tr>
<td>24 studies</td>
<td>756</td>
<td>18F-FDG-PET</td>
<td>93</td>
<td>58</td>
<td>51</td>
<td>86</td>
</tr>
<tr>
<td>13 studies</td>
<td>420</td>
<td>End-diastolic wall thickness on MRI</td>
<td>95</td>
<td>41</td>
<td>56</td>
<td>92</td>
</tr>
<tr>
<td>13 studies</td>
<td>420</td>
<td>Dobutamine stress MRI</td>
<td>74</td>
<td>82</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>13 studies</td>
<td>420</td>
<td>Late gadolinium enhanced MRI</td>
<td>84</td>
<td>63</td>
<td>72</td>
<td>78</td>
</tr>
</tbody>
</table>

Data were averaged by the number of patients. All studies defined hibernating myocardium on the basis of improved wall motion after recanalization. (Reproduced from Schinkel et al. 2007 with permission.)
4. Assessment of Cardiac Function

Cardiac function of patients with chronic coronary heart disease is assessed by echocardiography, radionuclide imaging, cardiac CT, cardiac MRI, or cardiac catheterization/ventriculography. Evaluation of cardiac function should be performed when coronary heart disease is strongly suspected, when new-onset heart failure or arrhythmias are noted, and when the treatment strategy needs to be changed, and it is also important for predicting the prognosis. An appropriate test should be chosen from among the various imaging modalities by taking into account the risks, benefits, contraindications, radiation exposure, and cost. This section mainly focuses on selection of noninvasive diagnostic imaging methods according to the disease state.

4.1 Assessment of Cardiac Function in Chronic Coronary Heart Disease (Table 55)

4.1.1 Echocardiography

Echocardiography is frequently used to assess cardiac function because it is noninvasive, simple, rapid, easy to repeat, safe, and low cost. It is widely used at the bedside, in the emergency room, and in the operating room. Cardiac function is often normal in patients with chronic coronary heart disease, but echocardiography is useful for detecting regional wall motion abnormalities and for differentiation from other conditions that cause chest pain, such as aortic stenosis. It is particularly useful if the patient has a heart murmur, a history of myocardial infarction, or signs of heart failure.

When transthoracic echocardiography is performed, right and left ventricular systolic and diastolic function is evaluated by using 2- or 3-dimensional echocardiography, pulsed and continuous Doppler, color Doppler, and strain analysis. The LVEF is obtained by the modified Simpson’s method, in which the end-diastolic and end-systolic left ventricular volumes are calculated by tracing the endocar-

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**Table 54. Recommendations and Levels of Evidence for Testing Methods to Evaluate Myocardial Viability**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radionuclide imaging to evaluate myocardial viability when determining the indications for revascularization in asymptomatic patients with coronary heart disease</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>III</td>
</tr>
<tr>
<td>Noninvasive imaging (radionuclide imaging, cardiac MRI, stress echocardiography, etc.) to evaluate myocardial ischemia and viability in patients with new-onset heart failure who have coronary heart disease without angina pain and no contraindications to revascularization</td>
<td>Ila</td>
<td>C</td>
<td>B</td>
<td>III</td>
</tr>
<tr>
<td>Cardiac MRI and stress echocardiography before revascularization in patients with heart failure who have coronary heart disease and are candidates for revascularization</td>
<td>Ila</td>
<td>B</td>
<td>B</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 55** lists the level of evidence for each test based on the data currently available.
Table 55. Recommendations and Levels of Evidence for Testing Methods to Evaluate Cardiac Function

<table>
<thead>
<tr>
<th>Echocardiographic evaluation of left ventricular function</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with suspected chronic coronary heart disease at initial presentation</td>
<td>II</td>
<td>B</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
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COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

dial contour in the apical 4-chamber view (and 2-chamber view for the biplane Simpson’s method). The Tachholz method,1120 in which left ventricular inner diameter shortening is calculated from measurement of the left ventricular internal dimension at end-diastole and end-systole, is inaccurate in patients with left ventricular wall motion abnormality or remodeling and is not recommended in such patients. Measurement of the left ventricular volume and LVEF by 3D echocardiography is as accurate as by cardiac MRI.1121 The Doppler method allows calculation of the stroke index and cardiac output. In recent years, evaluation of systolic function by tissue Doppler and strain analysis has shown high reproducibility, and even detection of slight cardiac dysfunction is possible.1122 Left ventricular diastolic function cannot be evaluated accurately by a single echocardiographic index and is therefore evaluated from a composite index. Left ventricular diastolic dysfunction is the first sign of myocardial ischemia and suggests microangiopathy in patients who complain of shortness of breath and chest pain.131,1122 Evaluation of right ventricular function by echocardiography is relatively easy for tricuspid annular plane systolic excursion (TAPSE) and the tricuspid annular lateral systolic velocity (S') measured by tissue Doppler imaging.1117,1124

4.1.2 Cardiac Radionuclide Imaging

Evaluation of cardiac function by cardiac radionuclide imaging with ECG-gated myocardial perfusion SPECT is performed using dedicated software for analysis of cardiac function. LVEF is assessed from the ventricular volume, and diastolic function is assessed from the differential volume curve. The reproducibility of cardiac function indices calculated from ECG-gated SPECT is high. During stress radionuclide imaging, transient left ventricular enlargement and a decrease in LVEF may be noted; these changes reflect transient myocardial ischemia and aid in the diagnosis of coronary heart disease without blood flow evaluation. In patients who cannot undergo exercise testing, a pharmacological stress test is performed. Adenosine is commonly used, but may induce bronchospasm in patients with asthma. In such patients, dobutamine or regadenoson (a selective A2A receptor agonist; not covered by health insurance)1128 should be used instead. ECG-gated SPECT is useful for evaluating cardiac function, but has the disadvantage of radiation exposure. Cardiac blood-pool scintigraphy can evaluate both left and right ventricular function, and may be used when it is difficult to perform evaluation by ECG-gated SPECT.

4.1.3 Cardiac MRI

The advantages of cardiac MRI are that it is not affected by bone or air and can capture moving images of the heart with high spatial resolution in any plane in any direction. Accurate measurement of left ventricular function can be performed in patients with myocardial infarction and left ventricular deformity and/or wall motion abnormality. Cardiac MRI is currently the most accurate modality for measuring left ventricular and right ventricular volumes, cardiac mass, and LVEF.1126-1129 When evaluation by echocardiography is difficult, cardiac MRI is the best alternative, especially for evaluating the right ventricle.668 LGE imaging with gadolinium contrast medium can identify myocardial fibrosis, and the distribution of the LGE helps to distinguish between ischemic and nonischemic myocardium and to assess myocardial viability.939,1127,1130

4.1.4 CT

When cardiac function is evaluated with ECG-gated
MDCT, accurate measurement of left and right ventricular volumes, cardiac mass, and LVEF is possible, as with cardiac MRI.\textsuperscript{1121, 1123} Assessment of cardiac function by cardiac MRI is the standard procedure to combine with CCTA, because cardiac MRI allows detailed measurement of cardiac function by ECG-gated image reconstruction without increasing the use of contrast medium or radiation exposure,\textsuperscript{1124} but CT evaluation has been less common because of the disadvantage of increased radiation exposure. However, cardiac MRI is expensive and imaging takes a long time, so the number of facilities where it is available remains limited.\textsuperscript{1131} Cardiac MRI is relatively contraindicated in patients with claustrophobia, pacemakers, or ICDs, and analysis of cardiac function by CT is useful in such patients.\textsuperscript{1135}

\section*{4.1.5 Cardiac Catheterization and Ventriculography}

Catheterization and ventriculography were previously considered the gold standards, but in recent years noninvasive methods such as cardiac MRI (which excels in quantitative assessment) have frequently been used to measure left ventricular function.

As an index of systolic function, biplane left ventriculography (LVG) is used to measure LVEF and assess regional wall motion.\textsuperscript{1136, 1140} The papillary muscles and trabeculae are within the contour of the left ventricular cavity on LVG. Accordingly, the calculated value tends to be an overestimation compared with the true luminal volume. In a study comparing LVG and cardiac CT with cardiac MRI as the standard, cardiac CT was more accurate than LVG for assessing global and regional left ventricular wall motion.\textsuperscript{1141} Impedance catheters do not require contrast medium and can be used to measure left ventricular volume and LVEF.\textsuperscript{1142, 1143} Cardiac output can also be measured by thermodilution. In addition to LVEF, dP/dt is another index of contractility. (dP/dt)/P is also used, which is obtained by adjusting for the effect of changes in preload and afterload.\textsuperscript{1144} The left ventricular stroke work can also be calculated from the pressure–volume curve. Indices of diastolic function include dP/dt obtained from measurement of left ventricular pressures using a catheter tip manometer and the time constant of left ventricular relaxation (T or r).\textsuperscript{1145, 1147}

\section*{4.2 Application to Chronic Coronary Heart Disease}

\subsection*{4.2.1 Assessment of Resting Cardiac Function}

Echocardiographic assessment of cardiac function is important for risk stratification of patients with chronic coronary heart disease, and it should be performed at the initial presentation of all patients with suspected chronic coronary heart disease.\textsuperscript{127}

Echocardiographic assessment of cardiac function is recommended for patients with chronic coronary heart disease who have OMI, abnormal Q waves, signs of heart failure, complex ventricular arrhythmias, or an undiagnosed heart murmur.\textsuperscript{121, 127, 1140, 1148} It was reported that when resting LVEF was <35\%, the annual mortality rate was >3\%.\textsuperscript{1129} Echocardiography enables evaluation of left ventricular systolic and diastolic dysfunction, as well as left ventricular morphology, and may allow determination of the etiology of heart failure. In patients without signs of left ventricular dysfunction, it is possible to evaluate left ventricular and left atrial enlargement and to determine the cause of chest pain due to noncoronary heart diseases, such as aortic stenosis, so that treatment indices can be selected and prognostic information can be obtained. It is also possible to estimate the pulmonary artery pressure, evaluate mitral regurgitation, identify left ventricular aneurysms, and detect left ventricular thrombi. Thus, echocardiography is useful for predicting the prognosis.\textsuperscript{1140}

On the other hand, assessment of cardiac function by radionuclide imaging or cardiac MRI can be considered in patients with OMI, abnormal Q waves, signs of heart failure, or complex ventricular arrhythmias who do not require evaluation of an undiagnosed cardiac murmur.\textsuperscript{1140, 1158, 1159}

Cardiac MRI is accurate for assessing ventricular function and also provides information on the morphology of the myocardium and heart valves. LGE MRI can identify undetected necrotic scars and viable myocardium.\textsuperscript{1130, 1152, 1153} Evaluation of cardiac function by cardiac CT is also useful. However, these 3 modalities mentioned are all more expensive than echocardiography. Although attempts have been made to reduce radiation exposure during cardiac CT and cardiac radionuclide imaging, these methods are still not recommended for patients with a low pretest probability of coronary heart disease or for adolescents.

Left ventriculography is indicated when evaluation by other modalities is considered difficult in patients who require coronary angiography.\textsuperscript{1154} Invasive measurement of the pulmonary artery pressure and cardiac output are recommended when clinical evaluation is inadequate in patients with combined heart failure and circulatory failure.\textsuperscript{1155, 1156} but their routine use is not recommended in normotensive patients with heart failure who respond to treatment.\textsuperscript{1157, 1158} In patients with normal ECG, long-term repeated assessment of cardiac function with echocardiography, cardiac radionuclide imaging, cardiac MRI, or cardiac CT is not recommended, provided they do not have OMI, no signs of heart failure, and no complex ventricular arrhythmias.\textsuperscript{1160} Also, periodic evaluation at intervals of less than 1 year is not recommended for patients with no changes in clinical manifestations or treatment strategy.

\subsection*{4.2.2 Assessment of Cardiac Function With Stress Loading}

\textbf{a. If Exercise Can Be Performed}

If exercise is possible but the ECG findings are nondiagnostic, assessment of cardiac function by cardiac radionuclide imaging or echocardiography is recommended.\textsuperscript{1140, 1158, 1159, 1163} If the patient has left bundle branch block or ventricular pacing, exercise/pharmacological stress radionuclide imaging or echocardiography is recommended.\textsuperscript{1164, 1165}

\textbf{b. If Exercise Is Impossible}

Pharmacological stress radionuclide imaging or echocardiography is recommended for patients with chronic coronary heart disease who cannot perform adequate exercise, irrespective of whether ECG changes are diagnostic or not.\textsuperscript{1140, 1158, 1159}

\subsection*{4.2.3 Cardiac Function Assessment During Regular Follow-up}

Assessment of cardiac function using echocardiography or radionuclide imaging is recommended for patients with signs of the onset/progression of heart failure or for patients with a history of interventions for myocardial infarction.\textsuperscript{1140} However, regular cardiac function assessment using echo-
cardiology or radionuclide imaging is not required in patients with no changes in clinical condition and who have a low risk of cardiovascular events.\textsuperscript{128}

\subsection*{4.2.4 Follow-up of Patients With Asymptomatic Myocardial Ischemia}

Follow-up evaluation at intervals of 2 years or longer using exercise/pharmacological stress radionuclide imaging, echocardiography, or cardiac MRI is useful in patients with a history of asymptomatic myocardial ischemia, providing there is a high risk of recurrent cardiac events, inability to perform adequate exercise, nondiagnostic ECG changes, or incomplete coronary revascularization. Follow-up evaluation using exercise/pharmacological stress radionuclide imaging, echocardiography, or cardiac MRI is not required within 5 years after CABG or within 2 years after PCI.\textsuperscript{128,316,1115}

\subsection*{4.3 Future Challenges}

In the nuclear cardiology field, assessment of cardiac function is not only possible with SPECT but also PET, enabling accurate evaluation by various modalities such as cardiac MRI and cardiac CT. In addition, assessment of cardiac function by 3-dimensional echocardiography has equal accuracy to these modalities and strain analysis, such as speckle tracking, can detect even a slight decrease in cardiac function at an early stage. In the future, it will be important to select these modalities appropriately by considering the risks, benefits, and cost-effectiveness, after evaluating the patient's clinical condition and pretest probability.

\section*{5. Prediction of Prognosis}

In the Framingham heart study, the annual mortality rate for chronic coronary heart disease was 4%\textsuperscript{1166}. In a registry study of 38,602 patients performed between 2003 and 2004 after aspirin, \( \beta \)-blockers, and statins had been introduced, the 1-year mortality rate was 1.9\% and the combined rate of cardiovascular death, myocardial infarction, and stroke was 4.5\%.\textsuperscript{1167} The mortality rate for coronary heart disease is lower in Japan than in many other countries, but it is currently increasing, unlike in the USA where the rate is decreasing.\textsuperscript{1168} Against this background, the clinical significance of each test for predicting prognosis is described in this section, based on overseas evidence and Japanese data.

\subsection*{5.1 Clinical Signs}

The history and physical findings can be used to predict the prognosis with no additional costs or additional risks to the patient. The presence of angina at rest, new-onset angina, worsening of angina, or dyspnea adds to the risk of death or myocardial infarction.\textsuperscript{1169} Among 5,712 patients with chronic coronary heart disease who underwent stress testing, the annual mortality rate was 2.4\% for patients who had angina without dyspnea vs. 6.4\% for patients who had dyspnea.\textsuperscript{1170} The incidence of cardiovascular events is high in patients with physical signs of heart failure and in patients with arteriosclerotic lesions of vessels other than the coronary arteries (carotid and lower limb arteries).\textsuperscript{1167}

\subsection*{5.2 Risk Scores}

Risk scores are lower in patients with chronic coronary heart disease than in those with ACS. A clinical study of lipid-lowering therapy showed that risk stratification could be performed by age, sex, smoking, OMI, diabetes mellitus, hypertension, prior revascularization, total cholesterol, and HDL-cholesterol.\textsuperscript{1171} In Japan, the Suita score has been reported, which stratifies the 10-year risk of developing coronary heart disease by scoring the age, sex, smoking, blood pressure, HDL-cholesterol, LDL-cholesterol, glucose intolerance, and family history of early-onset coronary heart disease.\textsuperscript{1172}

\subsection*{5.3 Biochemical Tests}

According to the AHA and CDC statements on inflammatory markers and cardiovascular disease, the established prognostic markers are total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, fasting glucose, and renal function (eGFR).\textsuperscript{113} In addition, high-sensitivity C-reactive protein,\textsuperscript{1174} BNP,\textsuperscript{1175} and troponin\textsuperscript{1176} have been attracting attention as new biomarkers.

\subsection*{5.4 Exercise ECG}

Exercise ECG is not only useful for diagnosing myocardial ischemia, but also for predicting prognosis. The ACC/AHA Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease states that patients with ST depression \( \geq \)2mm, stress-induced ST elevation, or induction of lethal arrhythmias by low stress are high risk and have an annual incidence of death or myocardial infarction \( \geq \)3\%, while patients with symptomatic ST depression \( \geq \)1mm are intermediate-risk and have an annual incidence of death or myocardial infarction ranging from 1\% to 3\%.\textsuperscript{640} The most important prognostic factor is the maximum tolerated exercise load, not the duration of exercise or occurrence of symptoms, and it is reportedly associated with the vital prognosis.\textsuperscript{1177}

\subsection*{5.5 Echocardiography}

Impairment of left ventricular function is reported to be an adverse prognostic factor. According to the ACC/AHA Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease, patients with an LVEF <35\% and coronary artery disease represent a high-risk group with an annual incidence of death or myocardial infarction \( \geq \)3\%, while patients with an LVEF of 35–49\% and coronary artery disease represent an intermediate-risk group with an annual incidence of death or myocardial infarction ranging from 1\% to 3\%.\textsuperscript{640} Detection of impaired regional wall motion and left ventricular dysfunction on stress echocardiography is reported to be an adverse prognosis factor.\textsuperscript{1160} On the other hand, if stress echocardiography shows no abnormal findings, the annual incidence of cardiovascular events is \(<\)1\%.\textsuperscript{1178}

\subsection*{5.6 Cardiac Radionuclide Imaging}

\subsection*{5.6.1 Myocardial Perfusion SPECT}

Many observational studies have shown that stress myocardial perfusion scintigraphy is useful for predicting the prognosis of coronary heart disease.\textsuperscript{1179} As the amount of
ischemic myocardium detected by stress myocardial perfusion SPECT becomes more extensive, there is a proportional increase in cardiovascular events, whereas prognosis is excellent with drug therapy if ischemia is negative.\textsuperscript{227} The indicators of a poor prognosis on stress myocardial perfusion SPECT include: (1) severe and extensive reduction of blood flow (affecting $\geq$20\% of the left ventricular myocardium),\textsuperscript{1186} (2) transient or persistent dilation of the left ventricular cavity,\textsuperscript{1187} and (3) decreased LVEF and increased ESV on ECG-gated SPECT. In a study of 5,183 patients who underwent stress myocardial perfusion SPECT, the 2-year incidence of cardiac death and myocardial infarction was 0.7\% per year in 2,496 patients without defects, which was lower than the incidence of 2.6\% per year in patients with defects.\textsuperscript{228} In addition, a study of 309 patients with suspected coronary heart disease and normal exercise perfusion imaging showed that cardiac death only occurred in 1\% of them during a 10-year period.\textsuperscript{1192}

The J-ACCESS study was a prospective cohort study of 4,031 patients who underwent ECG-gated stress myocardial perfusion SPECT and were followed for 3 years.\textsuperscript{229} Subsequently, the J-ACCESS 2 study was performed in 506 high-risk patients with asymptomatic type 2 diabetes mellitus,\textsuperscript{230} the J-ACCESS 3 study enrolled 431 patients with CKD,\textsuperscript{1188} and the J-ACCESS 4 study followed 494 patients who underwent stress scintigraphy before and after revascularization.\textsuperscript{231} The J-ACCESS study showed that the incidence of events was much lower in Japanese patients ($=1/3$) than in Western patients (4.3\% over 3 years).\textsuperscript{223} Particularly, the incidence of events was extremely low in patients with normal stress ECG-gated SPECT (0.81\% per year in patients with normal myocardial blood flow, 0.67\% per year in patients with normal myocardial blood flow + normal ESV, and 0.61\% in patients with normal myocardial blood flow + normal ESV + normal LVEF), indicating that normal findings on stress ECG-gated SPECT were associated with an extremely good prognosis.\textsuperscript{1184} It was also reported that a negative result on stress ECG-gated SPECT is associated with a good prognosis, regardless of the pretest probability.\textsuperscript{1188}

The J-ACCESS study showed that an LVEF $\leq$45\%, summed difference score (SDS) $\geq$2, age, history of revascularization, and diabetes mellitus were independent predictors of cardiovascular events.\textsuperscript{1186} These factors have also been reported as useful for predicting the onset of heart failure.\textsuperscript{1197} Furthermore, Yoda et al found a strong association between the severity of ischemia and cardiovascular events in Japanese patients in a single-center study.\textsuperscript{1188} Data from the J-ACCESS study were used to develop a risk model for the Japanese population, which allows the incidence of events to be predicted from the age, sex, diabetes mellitus, presence/absence of CKD, ischemic myocardial volume on SPECT, and the LVEF and ESV obtained from ECG-gated SPECT.\textsuperscript{1189,1190}

\subsection{5.6.2 Fatty Acid Metabolism Imaging}

In Japan, I-123 BMIPP imaging is covered by health insurance, and has been shown to have prognostic value. Zen et al reported that BMIPP imaging was a significant prognostic indicator in 677 patients with asymptomatic diabetes mellitus and PAD,\textsuperscript{449} and Nishimura et al identified an association between cardiac death and abnormal BMIPP accumulation in dialysis patients without obstructive coronary heart disease.\textsuperscript{1191} Moreover, Hashimoto et al reported that the severity of the BMIPP defect could predict the prognosis of patients with nonischemic heart failure and preserved left ventricular systolic function.\textsuperscript{1192}

\subsection{5.6.3 Sympathetic Nerve Imaging}

There have been many reports about the prognostic value of I-123-labeled MIBG. Nakata et al combined information from independent heart failure databases in Japan and identified an association between MIBG findings and prognosis in 1,322 patients with heart failure. Also, the heart-to-mediastinum ratio on MIBG imaging has been shown to be an independent predictor of fatal events, independent of the NYHA classification, LVEF, and BNP level.\textsuperscript{309}

\subsection{5.6.4 Evaluation of CFR by PET}

Measurement of the CFR by PET is the gold standard for assessment of myocardial ischemia.\textsuperscript{1193} CFR has been reported to be a prognostic indicator that is independent of defect severity, cardiac function, and CACS.\textsuperscript{470,1194}

\subsection{5.7 Cardiac CT}

\subsubsection{5.7.1 CACS}

The CACS is known to be useful for stratifying the risk of cardiovascular events. According to the ACC/AHA consensus document, investigation of 27,622 asymptomatic patients showed that the relative risk was increased by 4.3-fold in the case of CACS $100–400$, by 7.2-fold if the CACS was $401–900$, and by 10.8-fold if the CACS was $\geq1,000$.\textsuperscript{1195} The annual incidence of cardiac events was 0.1\% if the CACS was 0, 0.5\% if the CACS was 1–100, and 2.4\% if the CACS was $\geq100$.\textsuperscript{1196} Thus, the CACS is useful for risk stratification of asymptomatic, intermediate-risk patients. On the other hand, there have been few reports about the prognostic value of the CACS in symptomatic patients. In 3,924 patients with a CACS of 0, cardiovascular events occurred in 1.8\% during a mean follow-up period of 42 months, while 8.9\% of CACS-positive patients developed events.\textsuperscript{1197} Currently, many guidelines recommend using the CACS for risk assessment in intermediate-risk or low-risk patients who have diabetes mellitus or a family history of early-onset coronary heart disease.

\subsubsection{5.7.2 CCTA}

CCTA is the most widely used imaging modality in Japan. Advances in CT equipment have reduced radiation exposure and improved image quality, and many current clinical and diagnostic guidelines recommend CT-based diagnosis.\textsuperscript{486} Information obtained from CCTA includes the presence/absence of coronary artery stenosis,\textsuperscript{1198} assessment of plaque characteristics,\textsuperscript{1199} and assessment of ischemia by FFR-CT based on hydrodynamics and advanced computing.\textsuperscript{1200} The number of coronary vessels with stenosis, the number of plaques, and the plaque characteristics on CT have been used to predict the short-term prognosis as well as for predicting the long-term prognosis over 5 years or longer.\textsuperscript{537,1201,1202} Feutcher et al studied CCTA findings in 1,499 patients with long-term follow-up for an average of 7.8 years, and demonstrated a strong association between the severity of stenosis or plaque characteristics and the prognosis.\textsuperscript{1203} The relationship between FFR-CT, which uses advanced computing to calculate the FFR from CT images, and the long-term prognosis has not been clarified, but FFR-CT is expected to play a role as a gatekeeper for catheter examinations in the future.\textsuperscript{588,1204,1205} However,
further studies are needed to determine whether the long-term prognosis can be predicted.

### 5.8 Cardiac MRI

Detection of asymptomatic myocardial injury by LGE MRI has been shown to be useful for evaluating the prognosis of patients with ischemic heart disease. In patients with suspected ischemic heart disease and no history of myocardial infarction, Kwong et al reported that the presence or absence of LGE MRI was the strongest predictor of cardiac death or major adverse events, even after adjustment for other risk factors such as diabetes mellitus. Stress myocardial perfusion MRI has been shown to be useful for diagnosing ischemic heart disease in patients with chest pain and for predicting the future risk of ischemic heart disease, myocardial infarction, or cardiac death. Jahnke et al performed adenosine and dobutamine stress myocardial perfusion MRI in patients with ischemic heart disease and found a significantly higher incidence of cardiac death and nonfatal myocardial infarction (16.5% over 3 years) in the case of both tests being abnormal. In addition, cardiac death or acute infarction (16.5% over 3 years) in the case of both tests had a cardiac event-free rate of 98.1% per year.

### 5.9 Coronary Angiography

It is well known that the number of affected coronary vessels and left ventricular function influence the prognosis of patients with ischemic heart disease. The 5-year survival rate of patients with stenosis of the proximal left anterior descending artery is 90%, which is lower than that of patients with distal stenosis (98%). The SYNTAX score, obtained by adding lesion morphology to these items, is useful for selecting the optimal revascularization method. Patients with severe stenosis of the left main trunk, proximal left anterior descending artery, or left circumflex artery have a poor prognosis with medical therapy alone.

Coronary angiography provides anatomical information on the coronary arteries and is therefore useful for predicting the prognosis, but this method cannot assess the presence/absence of ischemia. Moreover, the extent of stenosis is determined relative to the proximal vessel as a control, so it is underestimated in patients with diffuse arteriosclerosis. It is also known that rupture of vulnerable plaque causing ACS (which affects survival), can occur at sites with <50% stenosis on coronary angiography. Thus, prediction of the prognosis by using the FFR and IVUS has attracted attention in the hope of overcoming these limitations of coronary angiography.

### 5.10 FFR

The FFR is an index of the functional severity of stenosis and is used to determine the indication for coronary revascularization. It shows the severity of stenosis at the time of examination and does not predict subsequent progression or destabilization of the lesion. However, in patients with chronic stable coronary heart disease, lesions that are negative for ischemia as proven by FFR are associated with fewer subsequent events and a better prognosis. The functional severity of stenosis detected by the FFR is not only influenced by the anatomical features of the lesion (lumen area, lesion length, and lesion morphology), but also by a number of other factors including the blood flow to the distal territory (i.e., the area perfused by the affected artery), the extent of collateral flow, and the presence of coronary microvascular obstruction and myocardial damage. A lower FFR value indicates more severe ischemia.

The FFR value for predicting the occurrence of events, including coronary revascularization, is ~0.8, but the value for predicting hard events (death and myocardial infarction) is lower, being ~0.50–0.65.

Approximately 15–20% of patients who undergo revascularization by PCI with stenting show little improvement in FFR, suggesting a poor prognosis after PCI. Inadequate improvement in the FFR results from problems related to the target lesion, such as poor stent expansion and dissection at the stent edge, as well as the presence of diffuse disease. Inadequate improvement in FFR is relatively common in patients with left anterior descending artery lesions, and is reported to be associated with CKD.

It may predict a poor prognosis independent of anatomical patency. It has been reported that the FFR value after stenting correlates with the FFR value before stenting; that is, a low FFR before treatment is a predictor of poor improvement in coronary blood flow by stenting. Determination of the FFR values for the 3 coronary arteries (3V-FFR) can be used to determine the total extent of functional myocardial ischemia. This method attempts to quantitatively evaluate the extent of coronary plaques by measuring the FFR in each of the 3 vessels and summing the values to determine whether the long-term prognosis can be predicted.

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Approximately 15–20% of patients who undergo revascularization by PCI with stenting show little improvement in FFR, suggesting a poor prognosis after PCI. Inadequate improvement in the FFR results from problems related to the target lesion, such as poor stent expansion and dissection at the stent edge, as well as the presence of diffuse disease. Inadequate improvement in FFR is relatively common in patients with left anterior descending artery lesions, and is reported to be associated with CKD.

It may predict a poor prognosis independent of anatomical patency. It has been reported that the FFR value after stenting correlates with the FFR value before stenting; that is, a low FFR before treatment is a predictor of poor improvement in coronary blood flow by stenting. Determination of the FFR values for the 3 coronary arteries (3V-FFR) can be used to determine the total extent of functional myocardial ischemia. This method attempts to quantitatively evaluate the extent of coronary plaques by measuring the FFR in each of the 3 vessels and summing the values to determine whether the long-term prognosis can be predicted.

#### Table 56. Recommendations and Levels of Evidence for Testing Methods to Predict Prognoses

<table>
<thead>
<tr>
<th>Testing Methods to Predict Prognoses</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial perfusion SPECT</td>
<td>I</td>
<td>A</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>I125, BMIPP</td>
<td>Ib</td>
<td>C</td>
<td>C2</td>
<td>IVa</td>
</tr>
<tr>
<td>I125, MIBG</td>
<td>Ib</td>
<td>B</td>
<td>C2</td>
<td>IVa</td>
</tr>
<tr>
<td>Myocardial perfusion PET</td>
<td>I</td>
<td>A</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>CACS</td>
<td>I</td>
<td>A</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>CTA (including plaque imaging)</td>
<td>Ia</td>
<td>A</td>
<td>B</td>
<td>II</td>
</tr>
<tr>
<td>FFR-CT</td>
<td>Ib</td>
<td>C</td>
<td>C1</td>
<td>IVb</td>
</tr>
<tr>
<td>FFR</td>
<td>I</td>
<td>A</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Stress ECG</td>
<td>I</td>
<td>C</td>
<td>B</td>
<td>IVb</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>I</td>
<td>A</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Cardiac MRI</td>
<td>Ib</td>
<td>C</td>
<td>C1</td>
<td>IVb</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>I</td>
<td>A</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>IVUS</td>
<td>Ib</td>
<td>C</td>
<td>C1</td>
<td>IVb</td>
</tr>
</tbody>
</table>

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.
calculate the 3V-FFR, and it has been reported that 3V-FFR is a prognostic indicator of ischemia that is independent of FFR.\textsuperscript{1218}

FFR is widely used clinically, but the invasive nature of this test limits the potential extent of usage. Evaluation of CFR by PET has recently become available and is also used to predict the prognosis.\textsuperscript{312,1219} It has been reported that approximately 30\% of patients show dissociation between the FFR and CFR when ischemia is evaluated.\textsuperscript{1219} Importantly, patients with a low CFR have a poor prognosis due to the presence of diffuse lesions and microvascular obstruction, even if the FFR is good.\textsuperscript{313,1218,1219}

### 5.11 IVUS

In the PROSPECT study,\textsuperscript{1220} 697 patients with ACS underwent IVUS of 3 vessels, including a nonculprit vessel, and 11.6\% of these patients had an event caused by rupture of plaque in the nonculprit vessel over a follow-up period of 3 years. Analysis by VI-IVUS showed that the presence of a thin fibrous cap, a lumen area $\leq 4.0 \text{ mm}^2$, and positive plaque in the nonculprit vessel over a follow-up period and 11.6\% of these patients had an event caused by rupture of plaque in the nonculprit vessel over a follow-up period.\textsuperscript{313} More than 2 of these factors caused events in patients who had $\geq 2$ of these factors.

Recommendations and levels of evidence for prediction of prognosis are shown in Table 56.

### 6. Deciding the Treatment Strategy

Treatment of chronic coronary heart disease includes basal drug therapy and exercise therapy, as well as PCI and CABG for revascularization of the coronary arteries. Essentially, the indications for revascularization should be decided from the presence or absence of myocardial ischemia. However, it was reported that only 45\% of elective PCI procedures involved advance evaluation of myocardial ischemia by stress testing.\textsuperscript{1221} In fact, it is common that treatment is carried out on the basis of imaging findings alone in the actual clinical setting. The FAME study compared outcomes between patients with stable coronary heart disease and multivessel disease who underwent PCI for all significant organic stenoses vs. patients undergoing PCI for functional stenoses documented to cause myocardial ischemia, revealing a significant reduction of cardiovascular events in only the patients undergoing PCI for functional stenosis.\textsuperscript{124}

According to this background, the importance of proving the presence of myocardial ischemia has recently been highlighted with respect to selection of the treatment strategy. It is important to decide the treatment strategy by considering improvement of QOL and the prognosis, after determining the range and extent of myocardial ischemia using various examinations. Because there are racial differences in the underlying disease pathology, treatment decisions should ideally be based on the results of reliable clinical research performed in Japan. However, sufficient results have not been obtained yet. Accordingly, this section describes the various tests that are useful when determining treatment strategies for chronic coronary heart disease by reviewing the results of large-scale clinical studies conducted overseas and some Japanese data.

### 6.1 Coronary Heart Disease Without Myocardial Infarction

#### 6.1.1 Principles of Deciding the Treatment Strategy

In patients with coronary heart disease who have good left heart function and no history of myocardial infarction, the range and extent of myocardial ischemia should be determined by various tests, and risk stratification should be performed from the prognostic perspective. The treatment strategy should be selected by considering the patient’s comorbidities and age, such as whether to perform noninvasive treatment alone (including drug therapy) or invasive treatment, and whether to select PCI or CABG for invasive treatment. Progress in diagnostic imaging has been remarkable, leading to great improvement in the accuracy of evaluating coronary artery morphology by CT and MRA. Coronary angiography remains an essential procedure in the case of invasive treatment being considered. When the extent of stenosis is $\geq 75\%$ on coronary angiography, it is judged to be significant and invasive treatment should be considered. However, in principle, the treatment strategy should be decided after the presence of myocardial ischemia is verified by other methods.

#### 6.1.2 Significance of Tests Other Than Coronary Angiography for Selecting the Treatment Strategy

##### a. Noninvasive Tests

On exercise ECG, deep ST depression ($\geq 0.2 \text{ mV}$), a low exercise threshold for ST depression, and prolonged convalescent ST depression suggest severe myocardial ischemia. When the Duke treadmill score is calculated for prediction of the prognosis [(exercise duration) $- 5 \times$ (maximum ST depression mm) $- 4 \times$ (chest pain index) $- 0$ (if chest pain is absent; 1 if chest pain is present; and 2 if chest pain is the reason for stopping exercise)], a score of $-11$ or lower indicates a high risk and a score of $+5$ or higher indicates a low risk.\textsuperscript{5} However, it is impossible to identify the site of myocardial ischemia from the lead showing ST depression. In patients with bundle branch block, left ventricular hypertrophy, ventricular pacing, Wolff-Parkinson-White syndrome, or using digitalis preparations, there are limitations on determination of ST changes, with the sensitivity and specificity of exercise ECG being around 70\%.\textsuperscript{11}

Stress echocardiography and stress myocardial perfusion imaging allow the identification of regions of myocardial ischemia by detecting abnormal wall motion and myocardial perfusion abnormalities. According to the J-ACCESS study conducted in Japan, revascularization reduced cardiovascular events more effectively than drug therapy in patients with $>10\%$ of the myocardium affected by ischemia on myocardial perfusion imaging.\textsuperscript{300} Pharmacological stress myocardial perfusion imaging with agents such as adenosine is useful in patients who find it difficult to perform exercise. Imaging of the myocardial sympathetic nerves (I-123-MIBG) and myocardial fatty acid metabolism (I-123 BMIPP) may identify regions of myocardial ischemia.\textsuperscript{1222,1223} and these methods are particularly safe and useful in patients who have difficulty performing exercise. CCTA allows noninvasive morphological assessment of the coronary arteries and has increasingly been performed before coronary angiography in recent years. Its advantage is the ability to assess plaques and vascular remodeling as well as coronary artery stenosis.\textsuperscript{1224} As evaluation becomes difficult when lesions have severe calcification, a method for removing calcification based on the difference from

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noncontrast CT scans has been developed recently. Coronary MRA is not influenced by calcification, and it is possible to noninvasively evaluate coronary artery morphology without radiation exposure or use of contrast medium. Accordingly, widespread use of coronary MRA is expected in the future.

b. Invasive Tests
IVUS is useful for assessing plaque morphology and is also an excellent modality for detecting calcification. It provides accurate information on the vessel diameter at the lesion and reference sites, as well as about plaque localization. Recently, tissue characterization by IVUS has become available for clinical use and has been applied to coronary plaques. OCT has higher resolution than IVUS and is particularly good for visualizing the lumen and vessel walls. Delineation of plaque rupture, erosion, and calcified nodules is possible, as well as quantification of the thickness of the fibrous cap. Angioscopy allows direct observation of the inside of a blood vessel, so the presence/absence of thrombus and the color of the vessel wall can be examined. Arteriosclerotic lesions are often yellow, whereas normal vessel walls are white. Albeit invasive, this intra-vascular imaging modality provides valuable information for determining the PCI strategy.

The CFR is an indicator of the maximal increase in coronary blood flow from the resting state. A CFR ≤ 2.0 suggests functional coronary artery stenosis, but the value is also influenced by microangiopathy resulting from conditions such as diabetes, cardiac hypertrophy, and myocardial infarction. The FFR is calculated as the pressure at the distal end of a stenosis during drug-induced vasodilation divided by the aortic pressure. FFR < 0.75 indicating ischemia, 0.75–0.80 being borderline and FFR ≥ 0.80 is negative for ischemia. The DEFER study enrolled patients with an FFR ≥ 0.75 and compared outcomes between those with and without PCI after follow-up for 5 years. The incidence of cardiac death and myocardial infarction was 3.3% in the group without PCI and 7.9% in the group with PCI, confirming the absence of prognostic benefit from performing PCI.

c. Predicting the Prognosis by Cardiac Radionuclide Imaging
Stress myocardial perfusion scintigraphy can assess the range and extent of myocardial ischemia without the use of contrast medium and a wealth of data are available on the prognostic implications. In patients with stress-induced ischemia affecting ≥ 10% of the left ventricular mass on stress myocardial perfusion scintigraphy, it was reported that revascularization significantly reduced cardiac death compared with drug therapy alone. The J-ACCESS study conducted in Japan showed that cardiovascular events increased according to the volume of ischemic myocardium, and the prognosis of patients with ≥ 10% ischemic myocardium was better after revascularization than with drug therapy alone. The LVEF calculated by ECG-gated SPECT was also useful for risk stratification. As more evidence has been obtained in Japan, it has become possible to evaluate the risk for individual patients by using Japanese data.

6.2 Old Myocardial Infarction
6.2.1 Assessment of Cardiac Function
In patients with OMI, assessment of cardiac function is important for predicting the prognosis and deciding treatment strategies. Resting echocardiography is excellent for assessing cardiac function, and can be performed quickly and easily. Resting echocardiography allows evaluation of regional wall motion, left ventricular systolic and diastolic function, and valvular function. In OMI patients, ventricular wall thinning, aneurysm formation, and the presence/absence of left ventricular thrombus or remodeling can be assessed. MRI and ECG-gated cardiac radionuclide imaging are superior to echocardiography for evaluating regional wall motion and cardiac function, but also for assessing myocardial viability (discussed next). Accordingly, use of these methods has been increasing in recent years.

6.2.2 Evaluation of Myocardial Viability
a. Stress Echocardiography
Evaluation of myocardial viability in the infarct zone is important for predicting the prognosis and determining the indications for invasive therapy to treat culprit lesions. Akinesis on resting echocardiography does not always indicate irreversible necrosis of the myocardium. If hibernating myocardium is present in the affected region, cardiac function may be improved by revascularization. Improvement of wall motion after low-dose dobutamine challenge indicates myocardial viability. When the diagnostic accuracy of dobutamine stress echocardiography for myocardial viability was investigated, the sensitivity and specificity were reported to be 74–87% and 73–86%, respectively. Because methods based on visual evaluation are dependent on the evaluator’s subjective assessment and experience, objective evaluation methods such as tissue strain imaging are also being explored.

b. Cardiac Radionuclide Imaging
Myocardial perfusion SPECT with thallium or technetium is used to evaluate myocardial viability. In many reports, 50–60% of peak myocardial flow was used as the cutoff value for determining myocardial viability on the basis of resting myocardial blood flow. Combined use with ECG-gated SPECT for evaluation of wall motion improves diagnostic performance. Myocardial perfusion PET has superior spatial resolution to SPECT and better diagnostic performance with qualitative imaging. PET can be performed with 18F-FDG to evaluate myocardial viability. Myocardial blood flow can also be quantified, and CFR can be measured noninvasively using pharmacological stress.

c. MRI
LGE MRI achieves better contrast resolution than radionuclide imaging and can clearly delineate infarcted myocardium as high signal intensity areas. To perform stress myocardial perfusion MRI, coronary vasodilators such as adenosine are administered, and myocardial blood flow is assessed from the first-pass myocardial dynamics of gadolinium contrast medium. Cine MRI can be used to investigate regional wall motion by setting a cross-sectional view that is not affected by the lungs and other structures, allowing accurate evaluation of cardiac function. Thus, MRI can provide comprehensive assessment of the relationship between the ischemic/infarcted region and abnormal wall motion by comparing these various modalities.
6.2.3 Deciding the Treatment Strategy From Cardiac Autonomic Function

There is a strong relationship between the prognosis of patients with myocardial infarction or heart failure and the cardiac autonomic nervous system. Evaluation of sympathetic nerve activity includes measurement of the blood and urine levels of catecholamines and quantitative assessment of cardiac sympathetic nerves by I-123 MIBG myocardial sympathetic nerve imaging (cardio-mediastinal ratio of radioactivity and the washout rate). Evaluation of parasympathetic nerve activity is based on assessment of heart rate variability (high-frequency component detected by nonspectral or spectral analysis) and baroreceptor sensitivity.

6.3 Vasospastic Angina

The incidence of vasospastic angina is higher in Japan than in Western countries. The risk of sudden death is particularly high in patients with multivessel spasm, so a diagnosis is important. Vasospastic angina frequently occurs at night or early in the morning, and detection of ischemic changes on ECG at the time of attack is important for making a diagnosis. Therefore, Holter ECG should be performed for 24–48 hours as the first test. However, it is often difficult to detect ischemic changes during attacks in the real clinical setting. A cold stimulation test performed in the early morning can be useful for a diagnosis of vasospastic angina, as well as a hyperventilation test or exercise test. Imaging of myocardial sympathetic nerves (I-123-MIBG) or myocardial fatty acid metabolism (I-123 BMIPP) may identify regions of ischemia if severe myocardial ischemia occurs during attacks.

A coronary spasm provocation test by coronary angiography using acetylcholine or ergonovine provides direct visual confirmation of coronary spasm. To improve diagnostic accuracy, it is recommended that calcium-channel blockers and long-acting nitrates should be withdrawn for at least 48 hours, if possible. The criterion for a positive coronary spasm provocation test is transient total/subtotal occlusion (>90% stenosis) of a coronary artery associated with signs of myocardial ischemia (anginal pain and ischemic ST changes).

In patients with variant angina, the sensitivity and specificity of provocation testing with acetylcholine are high, being 89–93% and 100%, respectively. Because smoking and drinking are important risk factors for vasospasm, guidance about lifestyle modification is essential, such as cessation of smoking and reduction of alcohol consumption or abstinence from alcohol.

6.4 Asymptomatic Myocardial Ischemia

Asymptomatic myocardial ischemia is defined by objective evidence of myocardial ischemia in the absence of symptoms.
suggested angina, such as chest pain. In general, the classification of Cohn et al is used. Type I is asymptomatic myocardial ischemia without signs of myocardial infarction or angina pectoris, type II is asymptomatic myocardial ischemia occurring after myocardial infarction, and type III is asymptomatic myocardial ischemia accompanied by angina pectoris. Elderly patients, patients with diabetes mellitus, and patients with a history of myocardial infarction or revascularization are more likely to develop asymptomatic myocardial ischemia. A study using myocardial perfusion SPECT detected myocardial ischemia in 27% of asymptomatic patients without known cardiac disease.

Treatment of asymptomatic myocardial ischemia is similar to that of symptomatic ischemia; however, there are cases of improvement of QOL not being obtained after revascularization because the patient was asymptomatic. As with symptomatic myocardial ischemia, it is important to fully investigate the range and extent of myocardial ischemia using various tests and select the treatment strategy with the aim of improving QOL and the prognosis.

6.5 Future Challenges

Large-scale prospective studies on the investigation and treatment of coronary heart disease have recently been conducted in Japan, yielding clinical data on Japanese patients. Because there are racial differences in the pathology of coronary heart disease, it is desirable to accumulate more clinical data from Japanese patients in the future, in order to formulate treatment strategies based on the findings. Detection of vulnerable plaques at sites other than the culprit lesion is important for preventing ACS. Plaque instability does not always correlate with coronary artery stenosis, so tests for myocardial ischemia cannot detect vulnerable plaques. In the future, noninvasive modalities such as CCTA and MRA may be used for assessment of plaque characteristics.

Recommendations and levels of evidence for testing methods of selecting the treatment strategy are shown in Table 57.

7. Evaluating the Effect of Treatment

The aim of treating chronic stable coronary heart disease is to improve symptoms and the long-term prognosis. Various stress tests are used to assess the alleviation of myocardial ischemia or improvement of the threshold for induction of ischemia after treatment. Exercise tolerance is an objective predictor of the prognosis, and it was reported that the survival rate improves by 12% for each 1 Met increase in exercise tolerance. To assess the influence of treatment on the prognosis, improvement of prognostic factors is investigated. There are several clinical categories of coronary heart disease, and the tests used to assess the response to treatment vary among these categories. In this section, coronary heart disease is divided into 4 clinical categories: coronary heart disease without myocardial infarction, OMI, vasospastic angina, and asymptomatic myocardial ischemia. The role of various tests in evaluating the effect of treatment is described for each heart disease category.

7.1 Coronary Heart Disease Without Myocardial Infarction

7.1.1 ECG, Exercise ECG, Cardiac Radionuclide Imaging, and Stress Echocardiography

When evaluating the effect of treatment for coronary heart disease, confirming the improvement of symptoms and alleviation of myocardial ischemia are important. Successful treatment of ischemic heart disease, whether invasive or noninvasive, results in an increase in exercise tolerance. Stress echocardiography can assess the therapeutic effect on myocardial ischemia by confirming that wall motion abnormalities that existed before treatment are no longer detected. Exercise ECG is useful because it can simultaneously evaluate improvement of myocardial ischemia and exercise tolerance.

In patients who have coronary heart disease without myocardial infarction, assessment of myocardial hypoperfusion by exercise myocardial perfusion imaging is useful. However, because myocardial blood flow images obtained during exercise reflect the relative blood flow distribution, detection of coronary artery lesions may be difficult in patients with triple-vessel disease. TI-201 myocardial perfusion imaging is widely used for a diagnosis of ischemia, regional localization, assessment of severity, and prediction of the prognosis. Assessment of myocardial perfusion with Tc-99m-labeled agents has the same diagnostic value as TI-201 imaging, with the advantage of allowing simultaneous assessment of blood flow and wall motion by ECG-gated acquisition.

Imaging of myocardial fatty acid metabolism with I-123 BMIPP and imaging of myocardial sympathetic nerves with I-123-MIBG allow assessment of myocardial ischemia without stress loading by comparison with myocardial blood flow images obtained at rest. This approach is particularly useful in the elderly and in patients who cannot tolerate exercise. However, defects on I-123 BMIPP and I-123-MIBG images may potentially represent “ischemic memory”, reflecting myocardial ischemia that existed for several weeks prior to testing. Therefore, it is necessary to distinguish pretreatment “ischemic memory” from the effects of transient ischemia during treatment when these imaging modalities are used immediately after treatment. When I-123-MIBG myocardial sympathetic nerve imaging is performed, autonomic nervous system dysfunction in patients with diabetes mellitus or elderly patients often leads to decreased inferior wall accumulation even if myocardial blood flow is normal. Hence, care is required when evaluating the response to treatment by this imaging method.

Myocardial perfusion PET using N-13 ammonia or Rb-82 allows measurement of the CFR during perfusion imaging and is useful for determining the effect of drug therapy. In addition, imaging of myocardial glucose metabolism with 18F-FDG is useful for evaluation of myocardial viability.

7.1.2 CT, MRA, Coronary Angiography, FFR, and FFR-CT

Investigation of the coronary arteries is required in patients with anginal symptoms or suspected myocardial ischemia. Evaluation of coronary artery stenosis and the collateral circulation by coronary angiography is essential to determine the strategy for invasive treatment. Recent advances in CT have led to a rapid increase in its use for noninvasive imaging of the coronary arteries. CT has the advantage
that noninvasive assessment of the coronary arteries can be performed in patients who cannot undergo exercise testing with adequate load or in whom ischemia cannot be ruled out, and it is also used to characterize the coronary artery wall. Because of the requirement for ECG gating, it is difficult to perform CCTA in patients with tachycardia or arrhythmia. Coronary MRA has the advantages of avoiding radiation exposure and no requirement for contrast medium. Another advantage is that coronary artery calcification only has a small influence on images, but the technician needs to be experienced and skilled. Coronary angiography is an invasive procedure, which is appropriate when there is a strong suspicion of myocardial ischemia and the treatment strategy needs to be decided. Determining the FFR during coronary angiography is useful for evaluating myocardial ischemia. In general, revascularization is indicated if the FFR is <0.75, while an FFR of 0.75–0.80 is considered to be borderline.

On the other hand, there is limited evidence that the FFR is useful for evaluating the effect of treatment. In patients with implantation of bare metal stents, a significantly higher incidence of MACE was reported in the case of FFR <0.90 immediately after PCI. Medium- to long-term prognostic studies have shown that the incidence of MACE was significantly lower when FFR ≥0.86 and target vessel failure was significantly less frequent in patients whose FFR was ≥0.85 or ≥0.88. However, there are still many issues without consensus, such as whether an FFR cutoff value should be set for use immediately after PCI, whether additional PCI should be performed if the FFR is low, and whether the FFR should be tested immediately after PCI. FFR-CT has recently attracted attention and is suggested to be useful for evaluation of de novo lesions, but is not indicated for severely calcified lesions or stented lesions. According to the Japanese Circulation Society Guideline for Appropriate Use of FFR-CT, the diagnostic performance of FFR-CT for functional ischemia is not completely consistent with that of FFR, and further evidence is needed to clarify whether FFR-CT has equivalent diagnostic and prognostic value to FFR.

### 7.2 Old Myocardial Infarction
#### 7.2.1 Angina Pectoris or Myocardial Ischemia Associated With OMI
**a. Symptoms and ECG**
When OMI is complicated by effort angina, it is important to assess the patient’s symptoms in order to evaluate the effect of treatment. Exercise ECG and stress myocardial perfusion imaging can be used to determine the effect on exertional myocardial ischemia. The Japanese Society of Electrocardiology has issued the Antianginal Drug Evaluation Subcommittee Report on exercise ECG. The Society used improvement of ST depression at the same exercise time and improvement of exercise duration as the indices for judgment. In patients with OMI and abnormal Q waves, ST elevation on ECG during exercise loading may indicate myocardial ischemia or left ventricular asynergy. Although there are morphological differences in the elevated ST segments, it is not always easy to distinguish these conditions solely from the ECG findings.

Asymptomatic myocardial ischemia is not uncommon in OMI. The incidence of fatal myocardial infarction, heart failure, and overall mortality is comparable in patients with asymptomatic myocardial ischemia or symptomatic disease, which means that it is important to investigate the response to treatment. In patients with asymptomatic myocardial ischemia, Holter ECG and stress myocardial perfusion imaging are also used in addition to exercise ECG. The frequency of ST depression over 24 hours and the total duration of ST depression are used as indices for Holter ECG.

**b. Stress Myocardial Perfusion Imaging**
With stress myocardial perfusion imaging, the effect on myocardial ischemia can be comprehensively assessed from the presence and extent of transient perfusion defects, in addition to symptoms during stress loading and the ECG information. Many patients with myocardial infarction have hypoperfusion even at rest, and improvement of transient hypoperfusion during stress testing serves as an index for assessing the effect of treatment. This applies to both infarcted and noninfarcted myocardium. With TI-201 myocardial scintigraphy, both the size of the transient perfusion defect and the rate of tracer uptake in the hypoperfused area (%) uptake) are investigated. Te-99 m is superior to TI-201 for ECG-gated testing. The presence of a transient defect on stress myocardial perfusion imaging after revascularization generally indicates restenosis or graft occlusion. Even if ST depression is revealed by stress ECG in the period immediately after revascularization, myocardial perfusion imaging may still be normal. Moreover, transient defects can be seen on stress myocardial perfusion imaging even when the target vessel is patent. Such false-positive findings are common when arterial grafts are used for CABG. Thus, caution should be exercised when assessing restenosis after PCI or CABG. Higher sensitivity and specificity for restenosis can be obtained by performing stress myocardial perfusion imaging at 4–6 weeks after revascularization.

### 7.2.2 Left Ventricular Dysfunction With Myocardial Ischemia (Ischemic Cardiomyopathy)
**a. Left Ventricular Systolic and Diastolic Function**
Both multivessel disease and left ventricular dysfunction are independent indicators of a poor prognosis, so their combination results in a particularly poor prognosis. In these patients, the goal of treatment is to achieve improvement of myocardial ischemia and left ventricular function. The effect of treatment on myocardial ischemia is evaluated by the methods mentioned above.

In patients with left ventricular dysfunction due to myocardial ischemia, revascularization is aimed at improving cardiac function and reducing events. LVEF, an index of contractility, is often used to investigate improvement of cardiac function and is frequently measured by echocardiography. On the other hand, myocardial scintigraphy using ECG-gated SPECT and cardiac MRI can simultaneously evaluate left ventricular function and myocardial perfusion, so these methods are useful for assessing the response to treatment in patients with ischemic cardiomyopathy.

**b. Mitral Regurgitation**
Mitral regurgitation may occur in patients who have left ventricular dysfunction associated with myocardial infarction, and the prognosis is poor. Mitral regurgitation associated with chronic coronary heart disease is generally caused by functional mitral incompetence due to enlargement of the mitral annulus and papillary muscle dysfunction secondary to left ventricular remodeling. Because such
functional incompetence strongly correlates with the survival rate and incidence of heart failure, optimum medical treatment in accordance with the guidelines is essential. In addition, surgical treatment should be considered in patients with symptomatic mitral regurgitation. To assess the response to treatment, detection of mitral regurgitation and evaluation of its severity are performed by color Doppler imaging. In the case of assessment by transthoracic echocardiography being difficult to perform, transesophageal echocardiography may be performed instead.

### 7.2.3 Prevention and Treatment of Postinfarction Left Ventricular Remodeling

In some patients, myocardial scarring progresses to fibrosis after myocardial infarction, and then the left ventricle expands due to mural thinning in the infarct zone. Hypertrophy of cardiomyocytes in the noninfarcted areas and interstitial fibrosis also occur, resulting in impairment of left ventricular systolic and diastolic function. This process is called chronic postinfarction left ventricular remodeling and indicates a poor prognosis.

Acute left ventricular remodeling occurs from several weeks to months after myocardial infarction. However, left ventricular remodeling is a prolonged process in patients with chronic infarction, and it is therefore important to assess changes in left ventricular end-diastolic volume over time. At the same time, ESV, LVEF, left ventricular cardiac mass, left ventricular wall thickness, and myocardial viability should also be evaluated. Methods of assessing the response to treatment include echocardiography, ECG-gated myocardial SPECT, and cardiac MRI. Although echocardiography is simple and can be repeated easily, there are problems with inadequate spatial and temporal resolution. Cardiac MRI has the advantage of excellent spatial resolution and can measure the left ventricular volume and LVEF without radiation exposure. In addition, myocardial necrosis and fibrosis can be investigated by assessing LGE (Class IIa, Level B evidence).

### 7.3 Vasospastic Angina

Evaluation of the effect of treatment for vasospastic angina differs from that for stable effort angina, because the pathogenesis differs and there are differences in pathology and clinical features between the diseases. However, alleviation of chest pain and improvement of the prognosis are common treatment goals for both diseases. Chest pain is commonly assessed to evaluate the response to treatment, and judgment is based on the frequency of attacks and the duration of ST elevation. Accordingly, the effect of treatment can be determined from the ECG findings regardless of the presence/absence of chest pain. Patients with mild coronary spasm who do not have complete coronary artery occlusion by spasm may show ST depression at the time of attacks. Even if coronary spasm causes complete occlusion of the affected vessel, myocardial ischemia may remain endocardial and not become transmural due to development of collateral circulation, resulting in ST depression. Among the diagnostic imaging tests, myocardial I-123 BMIPP and I-123-MIBG imaging both have a high sensitivity and specificity for vasospastic angina and can be used to assess the response to treatment or to decide on the initiation or intensification of drug therapy. It has also been pointed out that vasospastic angina can show spontaneous remission, and it is important to determine the differences between patients who need to continue drug therapy and those who can reduce or cease it. However, it is difficult to assess the long-term effect of treatment for vasospastic angina, and discontinuation of drug therapy may lead to the onset of further attacks or sudden death. Therefore, caution should be exercised when reducing, suspending, or discontinuing drugs, even in patients with apparent spontaneous remission. The most important prognostic factor for vasospastic angina is a history of out-of-hospital cardiac arrest, followed by smoking, rest angina, significant organic stenosis, multi-vessel spasm, ST elevation during attacks, and use of β-blockers, and special attention should be paid to patients with these factors. Guidance to quit smoking is also important in patients with vasospastic angina.

Regarding the long-term prognosis of vasospastic angina, the 3-year survival rate was reported to be at least 96% in Japan. It was reported that progression to myocardial infarction is most likely to occur within a few months after the onset of vasospastic angina. Subsequently, the incidence of acute myocardial infarction is low and the clinical course is usually good, but it should be noted that sudden death may occur in some patients.

### 7.4 Asymptomatic Myocardial Ischemia

#### 7.4.1 Selection of Treatment

Asymptomatic myocardial ischemia is a condition in which transient myocardial ischemia is detected by various tests in the absence of anginal pain, and the Cohn classification is often used in the clinical setting. Although there is insufficient evidence to advocate periodic testing for the presence of asymptomatic myocardial ischemia, it is desirable to assess the response to treatment when a patient develops comorbidities or when progression of risk factors is suspected.

#### 7.4.2 Indices for Evaluation of Treatment

The main evaluation methods used in patients with asymptomatic myocardial ischemia are stress ECG, Holter ECG, stress echocardiography, and stress myocardial perfusion imaging. Patients with diabetes mellitus often have asymptomatic myocardial ischemia and myocardial infarction shows a worse prognosis when it is associated with diabetes mellitus. In patients with both angina pectoris and asymptomatic myocardial ischemia (Cohn type III), disappearance of symptoms should not be regarded as the only index for assessing the response to treatment. Tests for determining the effect of treatment on asymptomatic myocardial ischemia are described below. It should be noted that the tests selected will largely depend on the availability of equipment and skilled technicians.

#### 7.4.3 Exercise ECG

Exercise ECG is the most frequent modality for assessing
both the short-term and long-term effects of treatment. Cohn types II and III asymptomatic patients with positive exercise ECG are considered to be clinically equivalent to symptomatic patients with positive exercise ECG. If exercise ECG is negative or exercise tolerance is maintained, the prognosis is good and this serves as a guide for assessing the effect of treatment. The disadvantages of this method include it being limited to patients who can perform exercise, sufficient exercise loading is necessary, the ECG waveform needs to be determinable, and sensitivity is low.

### 7.4.4 Stress Myocardial Perfusion Imaging
Stress myocardial perfusion imaging can comprehensively evaluate the effect of treatment for myocardial ischemia based on the presence/absence and extent of transient perfusion defects, in addition to symptoms at the time of stress loading and ECG information. Accordingly, detection rate for ischemia is higher with stress myocardial perfusion imaging than with exercise ECG or stress echocardiography. Patients with restenosis after PCI are often asymptomatic, but a transient defect on stress myocardial perfusion imaging generally suggests restenosis or occlusion. This test is also useful in patients with asymptomatic occlusion of bypass grafts after CABG, particularly vein grafts.

Because reperfusion of nonviable myocardium does not improve the prognosis, evaluation of myocardial viability by stress myocardial perfusion imaging is also useful for deciding the treatment strategy. The incidence of cardiac events in patients with normal findings on stress myocardial perfusion imaging is approximately 0.6% per year in Japan and other countries, indicating that this method is also useful for predicting the prognosis.

### 7.4.5 Stress Echocardiography
After the onset of ischemia, wall motion decreases before symptoms or ECG abnormalities develop. Hence, stress echocardiography is useful for detecting ischemic events at the earliest possible timing. Even in patients with a positive result of treadmill exercise ECG, the incidence of cardiac events is low if wall motion abnormalities are not detected by stress echocardiography. In contrast, the probability of cardiac events is high in patients with wall motion abnormalities on stress echocardiography. Disadvantages of stress echocardiography are that determination of wall motion abnormalities is semiquantitative, and accurate evaluation depends on the experience and skill of the evaluator.

### 7.4.6 CCTA
CCTA has recently been used extensively in patients with asymptomatic ST changes and suspected ischemia. If adequate CT images can be obtained, for example by regulating the heart rate with a β-blocker, it is possible to determine the coronary artery diameter and assess plaques. Because of its high specificity, CCTA is a powerful tool for demonstrating the absence of coronary lesions. It is also effective for detecting stenosis, but is not so useful for evaluation of calcified lesions, and the requirement for contrast medium and radiation exposure is unavoidable.

### 7.4.7 Coronary Angiography
Coronary angiography is the most appropriate test for evaluating the anatomical features of the coronary arteries. However, clinical and functional indices have recently been considered more important than morphological indices in patients with chronic coronary heart disease, and there have been many reports that coronary angiography is unnecessary unless there are significant ischemic changes on exercise ECG or myocardial perfusion imaging. Moreover, the clinical significance of angiography in this setting has not been established, including its cost and effectiveness.
7.5 Arrhythmia

Myocardial infarction and myocardial ischemia are responsible for the development of various arrhythmias, including ventricular arrhythmias. If myocardial ischemia persists after treatment, it may lead to heart failure and sudden cardiac death, making alleviation of ischemia very important. Arrhythmias may be transient in the acute phase of ACS and do not necessarily require ongoing treatment, but OMI patients often have a substrate for ventricular arrhythmia. Therefore, care should be exercised if sustained ventricular tachycardia and/or ventricular fibrillation occur from 48 hours after the onset of myocardial infarction. In addition to symptoms, cardiac function and the presence/absence of ventricular tachycardia are important indicators for evaluating the effect of treatment and deciding the indications for ICD implantation.

A high incidence of atrial fibrillation (AF) has been reported in patients with coronary heart disease, particularly myocardial infarction. Tachycardia and arrhythmia due to AF give rise to worsening of cardiac function and coronary blood flow after myocardial infarction. The incidence of AF after myocardial infarction was reported to be 6–13%, with the risk factors being advanced age, heart failure, diabetes mellitus, etc. There have been many reports about the association between AF and ventricular tachycardia or death. Patients with myocardial infarction complicated by AF have a poor short-term and long-term prognosis.

The ESC Guideline for Management of Patients with Stable Coronary Heart Disease does not recommend Holter monitoring or arrhythmia provocation testing to detect arrhythmias in asymptomatic patients with chronic ischemic heart disease. However, arrhythmias may occur frequently in the early stage of myocardial ischemia and may be a risk factor for sudden death, heart failure, etc. It is also known that the mortality rate is high in patients with heart failure complicated by arrhythmia and patients with cardiac dysfunction. It is therefore worthwhile to test these patients even if they are asymptomatic.

### 7.6 Future Challenges

The algorithm for evaluation of the effect of treatment is...
summarized in Figure 25. As a result of treatment, there has been a remarkable improvement in the quality of methods for assessing the response to treatment. Nevertheless, in the era of extensive coronary catheter intervention, these diagnostic tests are overused in Japan. There are limited cost–benefit analyses to justify the use of these modalities and selecting strategies that are clinically and economically appropriate remains a major issue. Recommendations and levels of evidence for selecting treatment strategies and assessing myocardial ischemia are shown in Tables 57 and 58, respectively.

8. Diagnosis and Assessment in Children at High Risk for Coronary Heart Disease Including Kawasaki Disease

8.1 Target Diseases
Kawasaki disease is the main characteristic cause of chronic coronary heart disease in children. Other causes include congenital coronary artery anomalies, congenital heart disease, malformation syndrome, inborn errors of metabolism, and cardiac allograft vasculopathy. Many patients with these diseases have achieved long-term survival after receiving treatment during childhood. However, even if asymptomatic during childhood, coronary heart disease may develop in adulthood. Accordingly, ongoing management by a physician for adults is important. Coronary heart disease accounts for 24–31% of sudden deaths in children and young adults.\textsuperscript{1278,1279} The current school heart examination has limited value for detection of coronary disease, and caution should be required if chest pain or syncope occurs during exercise.

| 8.1.1 Kawasaki Disease |

Kawasaki disease (KD) is a vasculitic syndrome that usually occurs in infants and children aged 4 years or younger, and 2–3% of patients develop coronary artery aneurysms even if acute treatment is provided.\textsuperscript{1280} According to the Japanese nationwide survey,\textsuperscript{1281} the number of cases and incidence rate of KD continued to increase until 2015 and showed a slight decrease in 2016, with the annual number of cases being approximately 15,000. The prognosis of patients with coronary artery aneurysms is related to the internal diameter of the aneurysm. In patients with a measured aneurysm diameter ≤4 mm, there is little or no increase in IMT and stenotic lesions are rare.\textsuperscript{1282}

On the other hand, aneurysms ≥6 mm in diameter (especially in young children with a body surface area <0.5 m\textsuperscript{2}) are associated with a high risk of coronary artery stenosis.\textsuperscript{1283,1284} According to a recent study based on the z score, giant aneurysms with a z score ≥10 or actually measured at ≥8 mm had a worse prognosis (regression rate: 19%; incidence of coronary events: 34%; incidence of major cardiac events: 18–23%) than aneurysms with a z score <5 (regression rate: 87%; incidence of coronary events: 0%; incidence of major cardiac events: 0%).\textsuperscript{1285,1286}

| 8.1.2 Coronary Artery Anomalies |

Congenital coronary artery anomalies occur in approximately 1% of the general population and can be divided into anomalies of the origin/course, ostial stenosis/occlusion, anomalies of intrinsic coronary artery anatomy, and anomalous termination (Table 59).\textsuperscript{1287} Coronary artery anomalies are often associated with congenital heart disease, but may occur in apparently healthy children and can cause sudden death during exercise.\textsuperscript{1278,1279} In particular, the risk is high when the left coronary artery arises from the right coronary sinus and runs between the 2 great vessels, and this anomaly accounts for approximately one-third of sudden cardiogenic deaths in young adults.\textsuperscript{1278}

| 8.1.3 Congenital Heart Disease |

Coronary artery anomalies are commonly associated with anomalies of the great vessels and aortic valve, including complete transposition of great arteries, double outlet right ventricle, tetralogy of Fallot, and truncus arteriosus. Preoperative assessment of coronary artery anomalies should not be omitted, because it affects the procedure for cardiac surgery. Careful monitoring for coronary heart disease should be performed after coronary artery transplantation such as the Jatene procedure or the Ross procedure. Coronary artery stenosis/occlusion was reported in 4–17% of patients undergoing the Jatene procedure,\textsuperscript{1288} occurring in 40% and 7% of patients with or without signs of coronary heart disease, respectively.\textsuperscript{1289}

Table 59. Classification of Congenital Coronary Artery Malformations

<table>
<thead>
<tr>
<th>1. Abnormalities of the coronary artery origin and course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Origin from the aortic root</td>
</tr>
<tr>
<td>1.1.1 Single coronary artery</td>
</tr>
<tr>
<td>1.1.2 Abnormal origin close to the normal origin: high take-off, low take-off, and commissural ostium</td>
</tr>
<tr>
<td>1.1.3 Anomalous aortic origin of a coronary artery</td>
</tr>
<tr>
<td>a. Anomalous aortic origin of the left main coronary artery</td>
</tr>
<tr>
<td>b. Anomalous aortic origin of the right coronary artery</td>
</tr>
<tr>
<td>c. Anomalous aortic origin of a coronary artery from the noncoronary sinus</td>
</tr>
<tr>
<td>d. Other anomalies</td>
</tr>
<tr>
<td>1.2 Origin from sites other than the aortic root</td>
</tr>
<tr>
<td>1.2.1 Pulmonary artery</td>
</tr>
<tr>
<td>a. Anomalous left coronary artery arising from the pulmonary artery (Bland-White-Garland syndrome)</td>
</tr>
<tr>
<td>b. Anomalous right coronary artery arising from the pulmonary artery</td>
</tr>
<tr>
<td>c. Anomalous left anterior descending coronary artery arising from the pulmonary artery sinus</td>
</tr>
<tr>
<td>d. Anomalous left circumflex coronary artery arising from the pulmonary artery</td>
</tr>
<tr>
<td>e. Total anomalous origin of the coronary arteries from the pulmonary artery</td>
</tr>
<tr>
<td>1.2.2 Aortic arch and branches</td>
</tr>
<tr>
<td>2. Coronary artery ostial stenosis/atresia</td>
</tr>
<tr>
<td>2.1 Coronary artery ostial stenosis</td>
</tr>
<tr>
<td>2.2 Coronary artery ostial atresia</td>
</tr>
<tr>
<td>3. Anomalous coronary artery course</td>
</tr>
<tr>
<td>3.1 Myocardial bridge</td>
</tr>
<tr>
<td>3.2 Coronary artery duplication</td>
</tr>
<tr>
<td>3.3 Others: absent or hypoplastic coronary artery, subendocardial coronary artery, etc.</td>
</tr>
<tr>
<td>4. Anomalies of coronary artery termination</td>
</tr>
<tr>
<td>4.1 Coronary artery fistula</td>
</tr>
<tr>
<td>4.2 Coronary sinus anomalies: ostial atresia, absence/hypoplasia</td>
</tr>
</tbody>
</table>

(Reproduced from Angelini et al 2002,\textsuperscript{1287} with permission.)
Coronary artery anomalies may be seen in 22q11.2 deletion syndrome accompanied by great vessel anomalies and in Williams syndrome accompanied by supravalvular aortic stenosis. Williams syndrome is associated with a high incidence of coronary ostial stenosis (5-19%), as well as extensive stenosis, occlusion, or enlargement of the coronary arteries. Inborn errors of metabolism, such as familial hyperlipidemia and infantile systemic arterial calcification, cause children to have a similar risk of coronary heart disease as adults. In particular, improvement in the accuracy of genetic testing has shown that FH is more frequently associated with coronary heart disease than was realized hitherto.

### 8.2 Electrocardiography

#### 8.2.1 Exercise ECG
Exercise ECG is of great clinical significance because it is simple and relatively safe to perform in children. If resting ECG clearly suggests myocardial ischemia, whether stress testing should be performed needs to be carefully considered. Stress testing is high risk in patients with pulmonary hypertension, dilated and restrictive cardiomyopathy, hypertrophic cardiomyopathy accompanied by moderate left ventricular outflow tract stenosis (contraindicated for severe cases), and exercise-related syncope of unknown cause.

The Master 2-step test is a simple exercise loading method, but the double Master (3 min; commonly used in adults) may not be sufficient in children with a high exercise tolerance. In infants aged 3 years or older, the jump test, in which children jump at a given tempo, may also be used. Treadmill and ergometer tests can generally be performed in school-aged children. Use of a bicycle ergometer (which children ride at their own tempo) imposes less stress, but is safer. For detection of myocardial ischemia in patients with KD and coronary artery aneurysms, exercise stress ECG only has a sensitivity of 33-46%, and it is therefore better to combine exercise tests with diagnostic imaging as appropriate.

#### 8.2.2 Resting ECG, Holter ECG, etc.
Resting ECG and Holter ECG can even be performed in infants who cannot exercise. Attention should be paid to ST-T changes and abnormal Q waves. QT dispersion is reported to be high in patients with coronary lesions caused by KD. Extended ECG, including Holter monitoring, may be useful in the diagnosis of syncope, chest pain, or arrhythmias caused by myocardial ischemia. Although body surface ECG, SAE, and magnetocardiography have also been studied in children, these methods are not widely used in daily practice.

### 8.3 Echocardiography

#### 8.3.1 Resting Echocardiography
The noninvasiveness and rapidity of resting transthoracic echocardiography (TTE) are advantages for use in children. The coronary arteries of children can be easily visualized by TTE. Therefore, careful observation of malformations, including the origin and course, and measurement of the internal diameter, should be carried out. Echocardiography is also useful for assessing structural abnormalities of the heart, valvular disease, thrombosis, and systolic/diastolic function, but it has limitations for detecting myocardial ischemia.

For diagnosis of coronary artery dilatation/aneurysm, the normal internal coronary artery diameter has been defined <3 mm under the age of 5 years and <4 mm at age 5 or older in accordance with the literature on KD. (there are some reports in which it was ≤3 mm and ≤4 mm, respectively, but the source of data for children aged 5 years or older was unclear). According to a statement issued by the AHA in 2017 on the Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease, a z score <2.0 is defined as normal. Given that the normal value to calculate the z score has been established in Japanese children too, the z score is expected to be used more widely in the future.

According to the classification in the Japanese guidelines, an internal coronary artery diameter ≤4 mm is considered to represent dilation (or a small aneurysm), 4-8 mm is a medium-sized aneurysm, and ≥8 mm is a giant aneurysm, with the same management as for giant aneurysms being recommended in the case of diameter ≥6 mm. In another classification, dilation is defined as less than 1.5-fold of the peripheral coronary diameter, 1.5-4-fold is a medium aneurysm, and >4-fold is a giant aneurysm in children aged 5 years or older, and such classification is a type of body size-based correction. According to the AHA guidelines, a z score of 2 to <2.5 (or a decrease of at least 1 during follow-up if initially <2) indicates dilation, from 2.5 to <5 indicates a small aneurysm, from 5 to <10 with the actual measured value <8 mm indicates a medium aneurysm, and ≥10 or the actual measured value ≥8 mm indicates a giant aneurysm.

#### 8.3.2 Stress Echocardiography, etc.
In children, cardiac function and hemodynamics, including myocardial ischemia, are assessed by echocardiography with exercise or pharmacological stress. Dobutamine stress echocardiography can detect ischemic lesions in patients with KD and patients who have undergone the Jatene procedure for complete transposition of the great arteries. It is useful for predicting the long-term risk of major cardiac events in patients with KD. There have also been reports about using myocardial contrast echocardiography and 3-dimensional echocardiography for KD.

### 8.4 Myocardial Perfusion Imaging

#### 8.4.1 Target Diseases

a. Kawasaki Disease

In children, myocardial perfusion imaging is often used to investigate coronary artery lesions caused by KD. With regard to diagnostic imaging for follow-up of coronary artery lesions due to KD, an AHA statement recommends selecting the methods and testing intervals according to the internal diameter of the coronary artery aneurysms. For patients with small or larger coronary artery aneurysms (z score ≥2.5), including medium and giant aneurysms, stress echocardiography, stress MRI, stress myocardial perfusion SPECT, and PET receive a Class IIa recommendation with evidence level B, and are designated as “reasonable” ischemia-inducing tests. It is stated that confirmation of the presence/absence of ischemia by stress testing is the most important objective of the examination. Stress myocardial perfusion SPECT is recom-
mended every 2–3 years for small coronary artery aneurysms, every 1–3 years for medium aneurysms, and every 6–12 months for giant aneurysms.

b. Coronary Artery Anomalies
In patients with coronary artery anomalies, myocardial perfusion imaging is sometimes used for preoperative assessment of anomalous origin of the left coronary artery from the pulmonary artery. Mismatch of myocardial blood flow and fatty acid metabolism, as well as improvement of myocardial blood flow in the early postoperative period, have been reported.

c. Congenital Heart Disease
The target patients are those who have received coronary artery transplantation by the Ross or Jatene procedure. In a study of 10 children aged ≤6 years who underwent the Jatene procedure for complete transposition of great arteries, no abnormalities were found by resting or adenosine stress myocardial perfusion SPECT. On the other hand, it was reported that coronary artery stenosis and occlusion occurred in 11.3% of patients after the Jatene procedure, and that myocardial perfusion SPECT showed no abnormalities in some patients despite the presence of left coronary artery ostial stenosis and ventricular fibrillation during follow-up.

8.4.2 Radiopharmaceuticals
The consensus guidelines for nuclear medicine studies in children recommend Tc myocardial perfusion agents (Tc-99 m sestamibi and Tc-99 m tetrofosmin) as standard pediatric agents in consideration of reducing radiation exposure. Thallium chloride, such as TI-201, is not recommended for children because the exposure dose in the myocardial perfusion stress/rest protocol is expected to be approximately 8–10-fold greater than that of Tc preparations.

8.4.3 Radiation Exposure
In the USA, 42.5% of children younger than 18 years have undergone radiography and 0.7% have undergone nuclear medicine studies, indicating that nuclear studies are not widely performed on children. In Japan, nuclear medicine studies performed in children aged 15 years or younger account for 3.4% of all nuclear medicine studies, and cardiac radionuclide imaging accounts for 2.5% of all nuclear medicine studies in children, so both percentages are quite low. However, children often require repeated examinations from infancy, especially those with coronary heart disease after KD, and cardiac radionuclide imaging from childhood could result in major cumulative exposure to radiation. A study of radiation exposure among adults in the USA found that overall medical radiation exposure increased from an effective dose of 0.54 mSv (1980–1982) to 3.0 mSv (2006), while radiation exposure from nuclear medicine studies increased from 0.14 mSv (1980–1982) to 0.77 mSv (2006), indicating that nuclear studies accounted for a high share of the overall medical radiation exposure.

In order to minimize radiation exposure during cardiac radionuclide imaging, it is important to use small doses in pediatric patients, use Tc myocardial perfusion agents, encourage post-test fluid intake and early voiding, and use the minimum dose that provides useful images for diagnostic purposes. In Japan, the relationship between image quality and the appropriate radiopharmaceutical dose is described in the consensus guidelines for nuclear medicine examination in children. It is also necessary to be aware of the characteristics of nuclear medicine studies. For example, the effective dose per unit dose and radiosensitivity both increase as the patient becomes younger. In addition, the half-life of TI-201 is very long at 73 hours, compared with 6 hours for Tc myocardial perfusion agents.

8.4.4 Pharmacological Stress Drugs
Pharmacological stress and resting myocardial perfusion SPECT is an important method for detecting coronary artery stenosis caused by KD. In Japan, adenosine is approved for nuclear medicine studies and is the main agent used for pharmacological stress. Usefulness of adenosine stress loading for evaluation of coronary stenosis caused by KD has been reported. Adenosine causes minor adverse reactions, but the incidence is high. However, given its short half-life of less than 10 s, it is useful for infants and young children, who tend to complain of symptoms less often and are therefore more likely to have latent disease.

8.4.5 Myocardial Perfusion Imaging With Tc Myocardial Perfusion Agents
An imaging protocol using Tc myocardial perfusion agents (Tc-99 m sestamibi or Tc-99 m tetrofosmin) has been proposed for coronary stenosis due to KD. The consensus guidelines for nuclear medicine examination in children should be consulted for the recommended dose. In order to obtain good images, the following points should be taken into consideration: (1) careful attention should be paid to avoiding body movement at the time of imaging, and repeat imaging must be considered if movement artifacts are found after imaging; (2) the maximum stress load should be maintained for ≥1 min following administration of a radiopharmaceutical for stress imaging; (3) excretion from the liver and gallbladder should be promoted by eating and drinking egg products, milk, and cocoa after administration of Tc myocardial perfusion agents; (4) imaging should be performed ≥30 min after administration of the radiopharmaceutical so that liver accumulation has washed out; (5) adopting a backstroke position with the left upper extremity raised (Monzen posture) during imaging minimizes artifacts at sites adjacent to liver accumulation; and (6) drinking soda immediately before imaging distends the stomach and reduces artifacts at sites adjacent to intestinal accumulation.

8.4.6 ECG-Gated Acquisition
ECG-gated acquisition allows simultaneous analysis of myocardial blood flow and cardiac function. Indices that can be analyzed by this method include left ventricular wall motion, the wall thickness change rate, left ventricular volume, LVEF, and left ventricular diastolic function. Postischemic myocardial stunning can be investigated in patients with severe coronary artery lesions due to KD and the viability of infarcted myocardium can be assessed. There are limitations on using this method in patients with a small heart (diastolic volume ≤50 mL), who are generally aged 6 years or younger.

8.4.7 Appropriate Radiopharmaceutical Dosages
According to the Guidelines for Drug Therapy in Pediatric Patients with Cardiovascular Diseases by the Japanese Circulation Society, the general formula for determining the minimum dose that provides useful images for diagnostic purposes is described in the consensus guidelines for nuclear medicine examination in children.
the pediatric dosage of a radiopharmaceutical is as follows: pediatric dosage = adult dosage × (age + 1)/(age + 7). In 2013, the Japanese Society of Nuclear Medicine issued consensus guidelines for nuclear medicine examination in children, making it possible to calculate recommended doses for each radiopharmaceutical. As shown in Table 60, the appropriate dose of a radiopharmaceutical can be calculated as the product of the “Basic dose established for each radiopharmaceutical” and the “Coefficients set by weight for each class”.

### 8.5 CCTA

#### 8.5.1 Target Diseases

**a. Kawasaki Disease**

With regard to diagnostic imaging for follow-up of coronary artery lesions due to KD, the AHA recommended in 2017 that the testing methods and intervals should be determined on the basis of the internal diameter of the coronary artery aneurysm. For patients with small or larger coronary artery aneurysms (z score ≥ 2.5), including medium and giant aneurysms, CCTA, coronary MRA, and selective coronary angiography receive a Class IIb recommendation with evidence level C, and are described as “further imaging” methods that “may be considered”. It is reasonable to perform CCTA and other morphological evaluations less frequently than stress testing for ischemia. It is recommended to consider CCTA every 3–5 years in patients with small coronary artery aneurysms, every 2–5 years in patients with medium coronary artery aneurysms, and once within 6 months of onset and every 1–5 months thereafter in patients with giant coronary artery aneurysms. CCTA has the advantage over coronary MRA of allowing observation of the entire coronary artery, including peripheral lesions. Although the disadvantages are radiation exposure and the need to use β-blockers as premedication for heart rate control, the latter has a short half-life intravenous β-blocker can be safely used in children with a high heart rate. In younger children, CCTA is easier to perform from the viewpoint of sedation. Other advantages of CCTA over coronary MRA are the shorter acquisition time and no requirement for special techniques to perform imaging and image reconstruction. The short imaging time and the fact that sedation is not needed are highly significant for children.

Severe calcification is a characteristic of coronary artery lesions caused by KD, and it is one of the main reasons for false-positive findings on CCTA. Thanks to improvements in CT equipment, however, diagnostic performance has become much better. CCTA is important for detection of ischemic lesions associated with coronary artery aneurysms and severe coronary artery stenosis. CCTA uses contrast medium to depict blood flow, and is useful for evaluating the collateral circulation that characteristically develops after the onset of KD. It was reported that CCTA might be more useful than selective coronary angiography for evaluating collateral circulation associated with total occlusion, although the study was not specifically about KD.

**b. Coronary Artery Anomalies**

The guidelines for appropriate use of cardiac CT from the 8 major American societies state that CT is the most appropriate test, on a 9-point scale, for assessing coronary artery anomalies in adults. Coronary artery anomalies show wide variation (Table 59), and interpretation of these anomalies in children requires knowledge of the normal variants of coronary artery anatomy. A study of coronary artery anatomy in 543 patients undergoing CCTA showed that variations in the number of diagonal and obtuse marginal arteries were common, with 10.9% and 3.5% of patients having a myocardial bridge and absent left main trunk (i.e., the left anterior descending artery and left circumflex artery originated directly from the aorta), respectively. Regarding anomalies of coronary artery size, right coronary artery dominance accounts for 89%. Regarding anomalies of coronary artery size, right coronary artery dominance accounts for 89%. Takayasu’s arteritis is a systemic vasculitis that is commonly known as macroangiitis. According to a case report, an adult patient, not a child, with Takayasu’s arteritis had coronary lesions.

#### 8.5.2 Radiation Exposure

As dual-source CT and area-detector CT have become widely available, the radiation exposure from CCTA has declined rapidly, making it suitable for follow-up examination even in infants and young children. The effective doses delivered by 3 types of CT scanners were studied in persons aged <18 years, revealing that it was 6.8 mSv for 64-row MDCT, 2.9 mSv for 64-row dual-source CT, and 1.0 mSv for 128-row dual-source CT. One of the reasons for the reduction in the exposure dose is use of high-pitch prospective ECG gating. For infants and young children, it is also important to reduce radiation exposure by using low tube voltage imaging at 80 kV.

When calculating the effective dose (mSv) for children, conversion factors for the effective dose cannot be used with the same dose–length product as for adults. Conversion...
The role of cardiac MRI in the diagnosis of chronic coronary artery disease, and to assess aneurysms and PCI is sometimes performed at a later stage. CCTA has come to play a role as a substitute for invasive, selective coronary angiography without breath-holding is the mainstream imaging method. According to the latest systematic review and meta-analysis, coronary MRA has a sensitivity of 89% and specificity of 72% for detection of significant stenosis, and the sensitivity is even higher with contrast enhancement (95% vs. 87% without contrast). On the other hand, the primary purpose of coronary artery imaging in children is to identify the origin and course of the arteries in patients with congenital heart disease, and to assess aneurysms and stenosis in patients with KD. In children, image quality is highly dependent on body size and heart rate

### 8.6 MRI and MRA

The role of cardiac MRI in the diagnosis of chronic coronary artery disease can be summarized by the following 3 items: evaluation of coronary artery morphology, myocardial tissue characterization, and evaluation of cardiac function and wall motion. Cardiac MRI was initially established in adults, but the objectives of examination and imaging techniques are different for children. This section describes the application of cardiac MRI in children.

#### 8.6.1 Evaluation of Coronary Artery Morphology

In adults, the primary objective of evaluating coronary artery morphology is to detect significant stenosis associated with arteriosclerosis. Currently, whole-heart coronary MRA using the steady-state free precession (SSFP) sequence without breath-holding is the mainstream imaging method. According to the latest systematic review and meta-analysis, coronary MRA has a sensitivity of 89% and specificity of 72% for detection of significant stenosis, and the sensitivity is even higher with contrast enhancement (95% vs. 87% without contrast). On the other hand, the primary purpose of coronary artery imaging in children is to identify the origin and course of the arteries in patients with congenital heart disease, and to assess aneurysms and stenosis in patients with KD. In children, image quality is highly dependent on body size and heart rate

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Age (mean)</th>
<th>Magnetic field strength</th>
<th>No. of sequenced coil channels</th>
<th>Method/ imaging area</th>
<th>Contrast medium</th>
<th>Sedation</th>
<th>Coronary artery visualization (coronary artery - reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor et al</td>
<td>CHD (TGA), 16</td>
<td>8.7–14.1 (10.8)</td>
<td>1.5</td>
<td>SSFP 5</td>
<td>FB/target</td>
<td>Gd-DTPA 0.2 mmol/kg</td>
<td>General anesthesia (1/16)</td>
<td>Proximal site, 72% (surgical findings)</td>
</tr>
<tr>
<td>Mavrogeni et al</td>
<td>KD, 20</td>
<td>7–12 (NR)</td>
<td>1.5</td>
<td>GRE 5</td>
<td>FB/target</td>
<td>None</td>
<td>None</td>
<td>Overall, 100% (CAG)</td>
</tr>
<tr>
<td>Greil et al</td>
<td>KD, 6</td>
<td>2.5–7.8 (4.6)</td>
<td>1.5</td>
<td>SSFP 5</td>
<td>FB/whole heart</td>
<td>None</td>
<td>Propofol, midazolam</td>
<td>Overall, 100% (CAG)</td>
</tr>
<tr>
<td>Takemura et al</td>
<td>KD, 35</td>
<td>0.6–6.6 (3.6)</td>
<td>1.5</td>
<td>SSFP (NR)</td>
<td>FB/target and whole heart</td>
<td>None</td>
<td>Triclofos sodium syrup + thiopental sodium</td>
<td>Proximal site, 86–97%; Overall, 60% (none)</td>
</tr>
<tr>
<td>Beerbaum et al</td>
<td>CHD, 40</td>
<td>2.6–25.8 (14.1)</td>
<td>1.5</td>
<td>SSFP 5</td>
<td>FB/whole heart</td>
<td>None</td>
<td>General anesthesia (10/40)</td>
<td>Proximal site, 90% (CAG, 12)</td>
</tr>
<tr>
<td>Tangcharoen et al</td>
<td>CHD, 100</td>
<td>0.2–11 (3.9)</td>
<td>1.5</td>
<td>SSFP 2–5</td>
<td>FB/whole heart</td>
<td>Gd-DTPA 0.2 mmol/kg</td>
<td>General anesthesia</td>
<td>Overall, 79% (surgical findings, 58)</td>
</tr>
<tr>
<td>Rajiah et al</td>
<td>CHD, 112</td>
<td>0.03–68 (17)</td>
<td>1.5</td>
<td>SSFP (NR)</td>
<td>FB/whole heart</td>
<td>None</td>
<td>Yes (&lt;7 years)</td>
<td>Proximal site, 99% (CAG, 13%; CCTA, 2%)</td>
</tr>
<tr>
<td>Tacke et al</td>
<td>KD, 63</td>
<td>12.5–18.6 (14.6)</td>
<td>1.5</td>
<td>SSFP (NR)</td>
<td>FB/whole heart</td>
<td>None</td>
<td>None</td>
<td>Proximal site, 100% (None)</td>
</tr>
<tr>
<td>Kim et al</td>
<td>KD, 17</td>
<td>0.2–24 (14)</td>
<td>1.5</td>
<td>SSFP 5/32</td>
<td>FB/target and whole heart</td>
<td>None</td>
<td>NR</td>
<td>Overall, 74% (CCTA)</td>
</tr>
<tr>
<td>Hussain et al</td>
<td>CHD, 48; KD, 1; CM, 1</td>
<td>0.05–18 (4)</td>
<td>1.5</td>
<td>SSFP 2–5</td>
<td>FB/target and whole heart</td>
<td>None</td>
<td>General anesthesia</td>
<td>Superior to echocardiography (angiogram or surgical record)</td>
</tr>
<tr>
<td>Silva Vieira et al</td>
<td>CHD, 40</td>
<td>2–12 (6)</td>
<td>1.5</td>
<td>SSFP 5</td>
<td>FB/whole heart</td>
<td>None</td>
<td>Gd-BOPTA</td>
<td>General anesthesia</td>
</tr>
</tbody>
</table>

CAG, coronary angiography; CCTA, coronary CT angiography; CHD, congenital heart disease; CM, cardiomyopathy; FB, free-breathing; Gd-BOPTA, meglumine gadopentetate; Gd-DTPA, gadodiamide sodium; GRE, gradient echo; KD, Kawasaki disease; NR, not reported; SSFP, steady-state free precession; TGA, transposition of the great arteries.

Factors are set for each body site, age (neonates, 1, 5, 10 years, and adults), and tube voltage (80, 100, 120, and 140 kV). A younger age and lower tube voltage both lead to a larger conversion factor.

### 8.5.3 FFR-CT

In KD, calcification and stenosis are often noted at the sites of coronary artery aneurysms, and PCI is sometimes performed at a later stage. CCTA has come to play a role as a substitute for invasive, selective coronary angiography when assessing the cardiovascular prognosis, but the FFR-CT cutoff value for functional ischemia does not precisely correspond to the FFR value. The Japanese Circulation Society has issued guidelines for the appropriate use of HeartFlow FFR-CT, stating that it should not be used for screening, if the patient is not a candidate for revascularization, and if the diameter of the target coronary artery is ≤2 mm. FFR-CT cannot be calculated for small coronary arteries with a diameter ≤2 mm, which limits its application in children.
group, and it was recommended that mid-systole be set for collection of data in children aged ≤2 years. Delineation of the coronary arteries was possible in 84 children, including 1 of 6 (17%) among those aged <4 months vs. 83 of 94 (88%) among those aged >4 months. Another study of coronary MRA in 112 patients with congenital heart disease reported that the coronary artery origins were identified in 99%, although image quality was inferior in younger patients. Among 40 patients with congenital heart disease undergoing coronary MRA, the origin and proximal course of the right coronary artery were identified in all 40 patients, while this was achieved for the left main trunk and left anterior descending artery in 38 patients, and for the left circumflex artery in 36 patients. Segmental visualization was investigated in 35 patients with KD undergoing coronary MRA, showing that evaluation of the right coronary artery and the left main trunk and proximal left anterior descending artery was possible in 97%, while the proximal left circumflex artery was assessable in 91%. In 16 patients with complete transposition of the great arteries who had undergone the Jatene procedure, coronary MRA obtained useful images of 23 of 32 coronary arteries (72%).

As conditions such as the use of contrast medium, sedation, and controlled respiration vary from case to case, a simple judgment cannot be made. However, if scanning is performed under certain conditions in children aged ≥2 months, evaluation of the origin and proximal course of the coronary arteries is possible. There is consensus that the same imaging protocols used for adults are sufficient for patients aged ≥28 years who do not require sedation.

8.6.3 Evaluation of the Myocardium

Investigation of myocardial characteristics by cardiac MRI mainly involves pharmacological stress perfusion studies for evaluation of ischemia and late gadolinium enhancement (LGE) to assess myocardial viability and inflammation. Adenosine is commonly used for stress perfusion studies, with dipyridamole as an alternative. In adults, a meta-analysis demonstrated diagnostic accuracy of cardiac MRI for ischemia, with a sensitivity of 90% and specificity of 85% compared with FFR. Cardiac MRI has also been reported as useful for detecting ischemia in children, with a positive predictive value of 80% and negative predictive value of 88% compared with coronary angiography, as well as a positive predictive value of 78% and negative predictive value of 98% for MAC during 1-year follow-up. Another study showed that 4 of 15 children with KD and coronary artery aneurysms developed stress perfusion defects (5 had LGE), suggesting the usefulness of comprehensive evaluation by cardiac MRI, including coronary MRA/myocardial properties/wall motion.

Investigation of LGE is used for delineation of infarcts and assessment of myocardial viability in patients with KD and in patients who have undergone the Jatene procedure for complete transposition of the great arteries. Assessment of LGE is useful for differentiation of ischemic and nonischemic cardiomyopathy based on its distribution and extent, and this imaging method is fundamentally handled the same way as in adults.

8.6.3 Evaluation of Ventricular Function and Wall Motion

Imaging is performed in the same way as in adults to quantify wall motion, volumes, and cardiac mass. Usually, images are obtained with breath-holding, but when sedation is required in a child who cannot cooperate, motion artifacts should be reduced by partly fixing the abdomen to minimize chest movement during respiration and by summation of ≥2 images.

8.6.4 Sedation

In infants under 6 months old, scanning is possible during sleep after breast feeding, but the scanning protocol should be compatible with shallow sleep and a short imaging time. As shown in Table 61, deep sedation is also useful, but adequate monitoring is required to avoid the risk of hyperventilation or aspiration. The Joint Declaration of the Japan Pediatric Society, Japanese Society of Pediatric Anesthesiology, and Japanese Society of Pediatric Radiology on sedation for MRI provides further details. Imaging under general anesthesia allows breath-holding and is very safe if performed by a trained team. However, it requires the services of an anesthesiologist and special medical devices that can be used in a magnetic field, and is accordingly quite expensive.

8.6.5 No Radiation Exposure

The disadvantages of cardiac MRI are its high cost and long imaging time, while its advantages are no radiation exposure and contrast medium is not always required. Recent large-scale studies have shown that exposure to even low doses of radiation at a young age is associated with an increased risk of cancer. For example, the risk of leukemia was increased by a dose of 0.036 mGy, and there was a 24% increase in the risk of cancer per CT scan during a 9.5-year follow-up period. Hence, there is a significant benefit in using cardiac MRI for children who require follow-up with repeat imaging.

8.6.6 Other Considerations

The presence of implanted medical devices should be determined before MRI, whether cardiac or not. When the history is unclear and an implanted device may potentially be present, simple X-ray examination of the whole body is useful. Gadolinium contrast media may also cause problems. Although the risk is generally lower than with iodinated contrast media, attention should be paid to allergic reactions that can range from extravasation to wheals and even anaphylaxis. Therefore, written consent to use contrast medium should be obtained before testing. NSF has also been reported as a serious complication. It is characterized by progressive, untreatable, and life-threatening widespread fibrosis affecting the skin, subcutaneous tissues, joints, skeletal muscles, and internal organs. NSF usually occurs in patients with renal impairment and an eGFR <30 mL/min/1.73 m². Other risk factors for NSF include renal transplantation, concurrent hepatic disease, and pre-inflammatory conditions. However, NSF is extremely rare, and is even less frequent in children than adults. Because of the low incidence of NSF among neonates and infants, despite their immature renal function, some centers use high doses of gadolinium contrast media, but it is preferable to use the lowest possible dose.

Moreover, it was recently reported that gadolinium contrast media can accumulate in the brain. Metallic gadolinium is toxic, but there have been no reports about toxicity when it is administered as a contrast agent, except for NSF. There was no increase in the incidence of treatment-related Parkinson's disease among 99,000 patients...
who received gadolinium contrast agents compared with 146,000 patients who did not.\textsuperscript{1365} Also, pathological examination of the brain at autopsy showed no degeneration after administration of gadolinium contrast medium.\textsuperscript{1364} The European Medicines Agency suggested discontinuation of the marketing of linear gadolinium contrast media in March 2017.\textsuperscript{1367} On the other hand, the US FDA issued a safety declaration 2 months later stating that gadolinium contrast media are not harmful to health,\textsuperscript{1368} but then issued a new warning in December 2017.\textsuperscript{1369} Thus, no consensus has been reached, even among experts, so it is necessary to carefully assess future developments.

Another safety consideration is protection of the ears, especially in neonates and infants, to avoid auditory damage from the loud noise associated with MRI.\textsuperscript{1329} Some centers ensure that infants wear headphones as well as earplugs. Infants and young children are predisposed to develop hypothermia or hyperthermia during examination,\textsuperscript{1370} and therefore monitoring of body temperature is important.

\section*{8.6.7 Clinical Application}

The AHA Guideline for KD\textsuperscript{1295} mentions the role of cardiac MRI in evaluation of the cardiovascular system. Because this disease generally affects infants, echocardiography under sedation is the standard method for assessment of coronary artery diameter and ventricular and valvular function in the acute phase. However, cardiac MRI is also indicated in later childhood, when visualization may be decreased if coronary abnormalities such as aneurysm formation are present. Evaluation of coronary artery morphology by coronary MRA is positioned as follows: “should be considered when symptomatic in patients whose coronary artery diameter has returned to normal, and should be considered periodically in patients with aneurysms or residual enlargement (Recommendation Class IIb).” On the other hand, evaluation of the myocardium (mainly assessment of ischemia by perfusion studies) is described as “should be considered when symptomatic regardless of coronary artery diameter (Recommendation Class Ila).”

The background to such guidance is that cardiac MRI is expensive and technically complex with limited evidence. Nevertheless, it may be useful for routine follow-up from later childhood onwards, because of its major advantage of no radiation exposure. As the anomalous origin of a coronary artery is an important cause of sudden death among juveniles, it is expected that the indications for cardiac MRI may be eventually expanded to screening for school children and athletes.

\section*{8.6.8 Future Challenges}

When cardiac MRI is used for assessment of chronic coronary heart disease in children, the imaging method and performance vary according to the patient, examiner, and equipment. Therefore, clinicians ordering these tests should be aware of which patients are suitable and to what extent testing is feasible. Cardiac MRI is especially challenging in the neonatal period and early infancy, when the patient is very small and the heart rate is high. However, no use of contrast agents, no radiation exposure, and noninvasiveness are significant advantages, especially in children, who have a high sensitivity to radiation and a long life expectancy. It is necessary for workers involved in the pediatric cardiovascular field to make efforts to establish more appropriate testing methods based on thorough understanding of these points.

\section*{8.7 Cardiac Catheterization}

\subsection*{8.7.1 Coronary Angiography}

Coronary angiography via cardiac catheterization is the gold standard for accurate diagnosis of chronic coronary heart disease in children. It is indicated for patients with moderate or severe coronary artery aneurysms, coronary stenosis or occlusion, and coronary artery anomalies (origin and course), etc., and it is particularly indicated in the case of catheter treatment or surgery being considered. Additional tests may also be performed, such as measurement of the coronary artery pressures or coronary flow velocity and IVUS.

On the other hand, the disadvantages of cardiac catheterization are invasiveness and radiation exposure. There is a risk of thromboembolism, perforation, vascular injury, and arrhythmia during the procedure, as well as postprocedural peripheral circulatory failure at the puncture site and pseudoaneurysm. General anesthesia may also pose a risk in young children. Use of cardiac catheterization is only recommended if less invasive assessment using CCTA or MRA is impossible.

\subsection*{8.7.2 Measurement of Intracoronary Pressure, FFR, and Coronary Flow Velocity}

Measurement of pressure and blood flow velocity is mainly performed for coronary artery lesions in patients with KD. Small aneurysms show normal time-averaged blood flow velocity, CFR, and shear strength, whereas giant aneurysms generate turbulent flow with a decrease in the time-averaged blood flow velocity, CFR, and shear strength.\textsuperscript{1372} FFR and CFR are decreased at sites of significant coronary stenosis and show improvement after PCI or CAGB.\textsuperscript{1373}

\subsection*{8.7.3 IVUS and OCT}

IVUS and OCT delineate the structure of the coronary artery wall by using echo signals and near-infrared light, respectively, and can be used to observe intimal thickening, luminal stenosis, thrombi, and calcification. In a study of coronary artery aneurysms in patients with KD,\textsuperscript{1323} intimal thickening was frequently observed in vessels with an internal diameter ≥24 mm. Virtual histology IVUS allows tissue characterization at sites of intimal thickening, including fibrosis, calcification, lipid components, and necrosis.\textsuperscript{1374} There has been a similar report concerning OCT in children,\textsuperscript{1375} so further studies are warranted to investigate the relationship of these findings with long-term arteriosclerotic lesions and cardiovascular events. Recommendations and levels of evidence for diagnosis of children at risk for coronary heart disease are shown in Table 62.

\section*{9. Diagnosis of Polyvascular Disease}

\subsection*{9.1 Polyvascular Disease}

It has recently attracted attention that coronary heart disease can be associated with cerebrovascular disease and/or PAD of the lower extremities. These conditions all originate from systemic arteriosclerosis (atherothrombosis), and it has been advocated that patients with involvement of multiple vascular beds should be comprehensively managed under the designation of polyvascular disease (multivascular disease and systemic arteriosclerosis).\textsuperscript{1376} A
### Table 62. Recommendations and Levels of Evidence for Testing Methods to Diagnose and Assess Children at High Risk for Coronary Heart Disease (Kawasaki Disease, etc.)

<table>
<thead>
<tr>
<th>Exercise ECG</th>
<th>COR</th>
<th>LOE</th>
<th>GOR (MINDS)</th>
<th>LOE (MINDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic Kawasaki disease without coronary lesions</td>
<td>IIb</td>
<td>C</td>
<td>C1</td>
<td>V</td>
</tr>
<tr>
<td>Asymptomatic Kawasaki disease with coronary lesions</td>
<td>Ila</td>
<td>C</td>
<td>B</td>
<td>V</td>
</tr>
<tr>
<td>Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure)</td>
<td>I</td>
<td>C</td>
<td>B</td>
<td>V</td>
</tr>
<tr>
<td>All patients with a suspected ischemic event</td>
<td>I</td>
<td>C</td>
<td>B</td>
<td>IVb</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resting echocardiography</th>
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<tbody>
<tr>
<td>Asymptomatic Kawasaki disease without coronary lesions</td>
<td>I</td>
<td>C</td>
<td>A</td>
<td>IVa</td>
</tr>
<tr>
<td>Asymptomatic Kawasaki disease with coronary lesions</td>
<td>I</td>
<td>C</td>
<td>A</td>
<td>IVa</td>
</tr>
<tr>
<td>Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure)</td>
<td>I</td>
<td>C</td>
<td>A</td>
<td>V</td>
</tr>
<tr>
<td>All patients with a suspected ischemic event</td>
<td>I</td>
<td>C</td>
<td>A</td>
<td>IVa</td>
</tr>
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</table>

<table>
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<tr>
<th>Stress echocardiography</th>
<th></th>
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<tr>
<td>Asymptomatic Kawasaki disease without coronary lesions</td>
<td>IIb</td>
<td>C</td>
<td>C2</td>
<td>V</td>
</tr>
<tr>
<td>Asymptomatic Kawasaki disease with coronary lesions</td>
<td>I</td>
<td>C</td>
<td>B</td>
<td>IVa</td>
</tr>
<tr>
<td>Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure)</td>
<td>I</td>
<td>C</td>
<td>B</td>
<td>V</td>
</tr>
<tr>
<td>All patients with a suspected ischemic event</td>
<td>I</td>
<td>B</td>
<td>A</td>
<td>IVb</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Myocardial perfusion imaging</th>
<th></th>
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<tbody>
<tr>
<td>Asymptomatic Kawasaki disease without coronary lesions</td>
<td>IIb</td>
<td>C</td>
<td>C2</td>
<td>V</td>
</tr>
<tr>
<td>Asymptomatic Kawasaki disease with regression of coronary lesions</td>
<td>Ila</td>
<td>C</td>
<td>C1</td>
<td>V</td>
</tr>
<tr>
<td>Asymptomatic Kawasaki disease with coronary lesions</td>
<td>I</td>
<td>B</td>
<td>A</td>
<td>IVb</td>
</tr>
<tr>
<td>(Imaging at rest only): detection of anomalies of coronary artery origin and course (especially preoperative assessment)</td>
<td>Ila</td>
<td>C</td>
<td>C1</td>
<td>V</td>
</tr>
<tr>
<td>Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure)</td>
<td>I</td>
<td>C</td>
<td>B</td>
<td>V</td>
</tr>
<tr>
<td>All patients with a suspected ischemic event</td>
<td>I</td>
<td>B</td>
<td>A</td>
<td>IVb</td>
</tr>
</tbody>
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<table>
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<th></th>
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<tbody>
<tr>
<td>Asymptomatic Kawasaki disease without coronary lesions</td>
<td>IIb</td>
<td>C</td>
<td>C2</td>
<td>V</td>
</tr>
<tr>
<td>Asymptomatic Kawasaki disease with regression of coronary lesions</td>
<td>Ila</td>
<td>C</td>
<td>C1</td>
<td>V</td>
</tr>
<tr>
<td>Asymptomatic Kawasaki disease with coronary lesions</td>
<td>Ila</td>
<td>C</td>
<td>B</td>
<td>IVb</td>
</tr>
<tr>
<td>Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure) in younger children (approximately &lt;5 years old) requiring sedation</td>
<td>IIb</td>
<td>C</td>
<td>C1</td>
<td>V</td>
</tr>
<tr>
<td>Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure) in older children (approximately ≥5 years old) requiring sedation</td>
<td>Ila</td>
<td>C</td>
<td>B</td>
<td>V</td>
</tr>
<tr>
<td>All patients with a suspected ischemic event</td>
<td>Ila</td>
<td>C</td>
<td>B</td>
<td>IVb</td>
</tr>
</tbody>
</table>

(Table 62 continued the next page.)
prospective multicenter observational study of atherothrombosis (REACH Registry), showed that patients with atherothrombosis in the coronary, cerebral, or peripheral arteries often also have lesions in other vascular beds.\textsuperscript{1377, 1379}

It is important to note that the prognosis of patients with polyvascular disease is poor. A follow-up investigation of the REACH Registry study showed that the 1-year incidence of cardiovascular events increased with the number of affected vascular beds in patients with polyvascular disease.\textsuperscript{1167} Specifically, the incidence of cardiovascular events was 12.58\% in the case of 1 vascular bed being involved, but increased to 21.14\% when 2 beds were involved and to 26.27\% when 3 beds were involved. Thus, the incidence of events increased significantly along with the number of vascular beds involved (P<0.001). Furthermore, multivariate analysis of 4-year follow-up data from the REACH Registry showed that polyvascular disease was the most important risk factor for development of cardiovascular events (hazard ratio: 1.99; 95\% CI: 1.78–2.24).\textsuperscript{1380} Therefore, it is important to always be aware of the possibility of polyvascular disease when managing patients with coronary artery disease. It is also important to explore the possibility of polyvascular disease, including coronary artery disease, in patients who have cerebrovascular disease or PAD.

9.2 Cerebrovascular Disease (Table 63)

9.2.1 Significance as a Component of Polyvascular Disease

Cerebrovascular disease can be divided into ischemic cerebrovascular disorders (cerebral infarction and transient ischemic attack) and hemorrhagic cerebrovascular disorders (cerebral hemorrhage and subarachnoid hemorrhage). In Japan, the annual number of deaths from cerebrovascular disorders is \approx 110,000, and it is the fourth highest cause of death.\textsuperscript{1381} It is also the second most important reason for patients to require nursing care (18.4\%).\textsuperscript{1382} Prevention and appropriate treatment of the onset and recurrence of cerebrovascular disease are important.

In the REACH Registry study described above, cerebrovascular disease was identified in 16.9\% of patients with coronary heart disease.\textsuperscript{1378} It was reported that patients with a history of ischemic cerebrovascular disease have a higher incidence of recurrent cardiovascular events (adjusted hazard ratio: 1.52; 95\% CI: 1.40–1.65) than those without
such a history. Interestingly, patients with a history of ischemic cerebrovascular disease have a higher incidence of nonfatal cerebral infarction (adjusted hazard ratio: 3.06; 95% CI: 2.62–3.57). Hence, it is important to prevent the recurrence of cerebrovascular disease as well as coronary heart disease.

### 9.2.2 Symptoms and Physical Findings

The sudden onset of hemiplegia is the most typical symptom. However, various symptoms can occur, such as dysarthria, visual disorders, headache, nausea and vomiting, vertigo, and disturbance of consciousness. Accordingly, the potential development of cerebrovascular disorders should be considered in various situations. Patients with early cerebral infarction should receive prompt attention because they can be treated with intravenous recombinant tissue plasminogen activator (rt-PA) or intravascular therapy using a stent retriever.

### 9.2.3 Imaging Studies

Screening for cerebrovascular disease is performed by a combination of carotid ultrasound, head CT, head MRI, head and neck MRA, and/or CTA. Depending on the patient’s condition, cerebral perfusion scintigraphy or cerebral angiography may be added.

#### a. Carotid Ultrasound

Carotid ultrasonography is indicated under the following circumstances: (1) for diseases frequently associated with carotid stenosis and obstructive lesions or clinical findings suggestive of such diseases (hemiparesis, arterial bruit, diminished pulse, etc.); (2) when risk assessment is needed before invasive treatment of arteriosclerotic disease in other regions; and (3) in the presence of risk factors for arteriosclerosis and the potential for progression of arteriosclerosis. For evaluation of arteriosclerotic lesions, the maximum IMT of the right and left common carotid arteries, carotid bulb, and internal carotid arteries is measured. Assessment of stenosis in the common carotid artery is based on the severity of area stenosis, with diameter stenosis also being determined if necessary. For the internal carotid artery, the severity of stenosis is determined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. Measurement of blood flow (maximum blood flow rate, etc.) at the site of stenosis is also performed.\(^{1384}\)

#### b. CT

CT can be performed quickly. By using a contrast agent, it is possible to assess the presence and severity of stenosis, as well as the luminal morphology. Although calcification can be detected sensitively, observation of the lumen is difficult at sites of severe calcification. Disadvantages of CT include the risks associated with use of iodinated contrast medium and exposure to radiation. Indications for performing CTA in patients with cerebrovascular disease include arterial stenosis, aneurysms, arteriovenous malformations, sinus thrombosis, and dissection. Regarding the diagnostic accuracy for 70–99% stenosis at the carotid bifurcation, the sensitivity and specificity of CTA were reported to be 68% and 77%, respectively.\(^{1385}\)

#### c. MRI

MRI is used to evaluate the vessel lumen and wall. It allows visualization of the lumen without contrast agents by the TOF technique. Disadvantages of MRA include the long scan time, restrictions on use of equipment in the examination room/laboratory, and difficulty with interpretation of images due to artifacts. Although contrast medium may be used (contrast-enhanced MRA), the risks associated with gadolinium contrast media should be considered. In addition to the abovementioned indications for CTA in cerebrovascular disease, MRA can be used to screen for cerebral aneurysms and stenotic lesions.

Regarding the diagnostic accuracy for 70–99% stenosis at the carotid bifurcation, the sensitivity and specificity of MRA using the TOF technique without contrast medium were reported to be 76% and 86%, respectively, and contrast-enhanced MRA had a sensitivity and specificity of 86% and 91%, respectively.\(^{1385}\) The sequences for detecting vulnerable plaques in the carotid artery include T1-weighted, T2-weighted, and proton-density-weighted images, and these are often evaluated in combination. Magnetization prepared rapid acquisition with gradient echo (MPRAGE) is a T1-weighted imaging method that suppresses fat and blood flow signals, and it depicts plaque complicated by hemorrhage as a high signal area.\(^{1386}\)

#### d. Cerebral Angiography

Angiography involves advancing the catheter to the desired vessel for selective imaging. It provides images with excellent spatial and temporal resolution, but is an invasive test. Although it was reported that the risk of complications from cerebral angiography in patients with ischemic cerebrovascular disease is only in the order of a few percent,\(^{1387}\) this rate may be higher if asymptomatic cases are included.\(^{1388}\) Thus, the indications for angiography should be rigorously determined, and it is primarily limited to patients who require intravascular treatment and detailed perioperative assessment.
9.3 Peripheral Arterial Disease (Table 64)
9.3.1 Significance as a Component of Polyvascular Disease
The representative type of chronic peripheral obstructive arterial disease is ASO, which is caused by arteriosclerosis. The incidence of ASO has been increasing since the mid-1970s, overtaking thromboangiitis obliterans (so-called Buerger’s disease),1389 and it now accounts for a large part of PAD. In fact, the terms PAD and ASO are currently used almost synonymously. Among patients who have polyvascular disease, PAD is found in approximately half (55.3% in the REACH Registry;1378 49.5% in Japan1379). Conversely, approximately half of PAD patients have polyvascular disease (61.5% in the REACH Registry;1378 43.8% in Japan1379). This is higher than the prevalence of polyvascular disease in patients with coronary heart disease or cerebrovascular disease. Accordingly, the possibility of polyvascular disease should always be considered in PAD patients when plans for investigation are formulated. It should also be kept in mind that the all-cause mortality rate of patients with critical limb ischemia is as high as 80% at 5 years after an initial diagnosis.1389

9.3.2 Symptoms and Physical Findings
The diagnosis of PAD can often be made by taking a history, physical examination (inspection and palpation), or simple tests. It occurs most frequently in men aged ≥50 years. The characteristic symptom is intermittent claudication, and skin ulcers and necrosis can develop in severe cases. Symptoms include thinning of the affected extremity, decreased skin temperature and a difference from the other leg, skin pallor and cyanosis, nail deformity, hair loss, weak/absent pulses of the common femoral artery, popliteal artery, posterior tibial artery, and dorsalis pedis artery, a palpable thrill, and a vascular murmur. Control of risk factors is essential, and the presence/absence of smoking, diabetes mellitus, hyperlipidemia, or hypertension should be investigated accordingly.1389

9.3.3 Investigations
Among the following investigations, limb blood pressure measurement and imaging are usually combined. In addition to determining the ABI, an imaging test is essential. The appropriate test should be chosen according to the disease condition, with priority being given to minimally invasive methods.

a. Limb Blood Pressure Measurement
i) ABI
The ABI is used as an essential diagnosis of PAD, which is calculated as the systolic blood pressure at the ankle (posterior tibial artery and dorsalis pedis artery) divided by the higher of the right or left brachial systolic blood pressures. If the ABI is ≤0.90, significant stenosis of the main limb artery is suspected. If the ABI is >1.40, it indicates that the compression by a tourniquet is insufficient and the existence of severe arterial calcification is suspected.1389 The ACC/AHA guidelines define an ABI of 0.91–0.99 as the threshold value.1389 The ABI under exercise testing is used to assess the severity of intermittent claudication and to exclude neurogenic claudication.

ii) Toe Blood Pressure and TBI
Because calcification of the toe arteries is less severe than at the ankle, the TBI is more likely to provide accurate data than the ABI in patients who have severe arterial calcification, such as those with renal failure or diabetes mellitus. The cutoff value of the TBI is 0.6–0.7.1391

b. Imaging Studies
Conventionally, invasive angiography was the main modality of screening and preoperative assessment for PAD, but ultrasound, CT, and MRI have come to play a central role in recent years.

i) Ultrasound
Ultrasound is a noninvasive examination that can be performed at the bedside without exposure to radiation or use of contrast medium. In addition to evaluating the vessel wall and lumen, assessment of hemodynamics is available by the color Doppler or pulse Doppler method utilizing the high temporal resolution of ultrasound. Especially in patients with a morphologically borderline lesion, ultrasound is crucial for assessing whether stenosis is hemodynamically significant or not. However, ultrasound has some disadvantages: imaging quality depends on the skill of the technician, there can be difficulty in observing the iliac artery if there is massive bowel gas, and difficulty in overall and definitive assessment of the femoral artery due to the length of the observation area.1391

ii) CT
CT is a minimally invasive imaging modality, but it involves exposure to radiation and there is a risk of complications associated with use of iodinated contrast medium. CT is recommended in assessing vascular disease because of simultaneous assessment of the great vessels and parenchymal organs in addition to evaluation of the peripheral vasculature.1392 Both noncontrast CT scans and scans performed in the early contrast phase are required, because noncontrast scanning is crucial for assessing calcification of the arterial wall, whereas the vessel lumen is assessed on early contrast phase scans. In relation to the diagnostic performance of CTA using an MDCT scanner with 16 rows or more, the sensitivity and specificity were reported to be 95.99% and 94.98%, respectively.1393,1394 Although CT is useful for evaluating vessel wall properties, including

| Table 64. Recommendations and Levels of Evidence for Testing Methods to Diagnose PAD |
|-------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **COR** | **LOE** | **GOR (MINDS)** | **LOE (MINDS)** |
|------------------|------------------|------------------|------------------|------------------|------------------|
| ABI | I | B | B | IVa |
| TBI | Ila | C | C1 | IVb |
| Ultrasonography | I | C | C1 | IVb |
| CTA | I | C | B | IVb |
| MRA | I | C | B | IVb |
| Angiography | I | C | C1 | VI |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.
calcification, accurate assessment of the lumen may be difficult in patients with heavily calcified lesions or with stents. To overcome this weakness, new imaging methods such as subtraction techniques have been developed.iii195–197

iii) MRI
MRI has the advantage of being able to evaluate the vessel lumen without using radiation and is not influenced by calcification; however, its spatial resolution is inferior to CT. Moreover, MRI may be contraindicated in patients with a medical device or implant, so confirmation of safety is crucial.191

Imaging sequences for the diagnosis of PAD can be divided into contrast-enhanced MRA and noncontrast-enhanced MRA. With a sensitivity of 97% and specificity of 96%, the diagnostic accuracy of contrast-enhanced MRA is comparable to that of CTA.1398 Contrast-enhanced MRA is less susceptible than noncontrast-enhanced MRA to the influence of blood flow velocity, direction, and turbulence, and relatively rapid imaging of a wide area is possible.1391 On the other hand, use of gadolinium contrast media comes with a risk of NSF,1399 and alternative modalities should be considered in patients with renal dysfunction. Use of contrast-enhanced MRA should be carefully decided because many patients with PAD are elderly and have poor renal function.

Noncontrast-enhanced MRA is an alternative to contrast-enhanced MRA for assessment of lower limb arteries without using contrast medium. In addition to the conventional time-of-flight technique, methods such as fresh blood imaging are applied clinically. Compared with contrast-enhanced MRA, the sensitivity and specificity of noncontrast-enhanced MRA are reported to be 85.4% and 75.8%, respectively.1400 However, it has limitations regarding accurate delineation of small arterial lesions and assessment of luminal changes in metallic stents.1394,1401

iv) Angiography
Angiography can selectively evaluate the vessel lumen after inserting a catheter into the target artery and administering contrast medium directly into the vessel. It is an invasive procedure with a risk of bleeding and embolic complications. Other risks include exposure to radiation and complications associated with the use of iodinated contrast medium. Angiography is excellent for morphological diagnosis of stenosis and occlusion because of its high spatial resolution. It can also be used to evaluate blood flow dynamics. Furthermore, angiography allows assessment of hemodynamics by measuring the pressure gradient between proximal and distal to a lesion, and is used to guide intra-vascular treatment.194

Conclusion
As discussed, recent advances in diagnostic imaging for cardiovascular disease have been remarkable. In fact, the number of noninvasive imaging tests performed for chronic coronary heart disease in clinical practice has steadily increased over the past few years. Invasive procedures have also been used in many clinical fields, together with advances in technology. Both invasive and noninvasive methods may be required to provide important information that is directly relevant to understanding the patient’s pathophysiological situation and to the selection or monitoring of treatment.

It has also been pointed out that a number of revascularization procedures are performed for lesions detected by noninvasive imaging modalities such as CT, regardless of whether the patient has symptoms or ischemia (functional stenosis), raising alarm over increased healthcare expenditure due to advances in medical care. In recent years, confirmation of the existence of ischemia has been required before revascularization is performed in patients with chronic coronary heart disease. Accordingly, more efficient use of diagnostic imaging modalities are expected.

Imaging studies should be focused on assisting decisions about treatment and assessing the prognostic impact. However, more large-scale clinical studies are needed to provide sufficient data before imaging can properly fulfill these functions. Although sufficient evidence was not available in the past, a large body of evidence has recently been accumulated in both Japan and other countries. Taking these points into consideration, we compiled this guideline on the noninvasive diagnosis of chronic coronary heart disease, which is the condition with the highest incidence among all cardiovascular diseases, and efficient utilization of invasive examinations on the basis of the available evidence and the current medical practice in Japan. As a new feature, evidence-based recommendations have been added to each entry to facilitate the use of this guideline in clinical practice. Accordingly, we do hope that this guideline will be used in diverse clinical settings.

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<td>Koichi Node</td>
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<td>Atsushi Nohara</td>
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<td>Hironori Yekoi</td>
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### Potential COI of the participant

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<tr>
<th>Author</th>
<th>Potential COI of the participant</th>
<th>Employment / Leadership position (private company)</th>
<th>Stakeholder</th>
<th>Patent royalty</th>
<th>Honorary</th>
<th>Payment for manuscripts</th>
<th>Research grant</th>
<th>Scholarship (educational) grant</th>
<th>Embargo chair</th>
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### Potential COI of the head of the organization/department to which the participant belongs (when the participant is in the position of corporate research with the head of the organization/department)

<table>
<thead>
<tr>
<th>Author</th>
<th>Potential COI of the head of the organization/department to which the participant belongs (when the participant is in the position of corporate research with the head of the organization/department)</th>
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<tbody>
<tr>
<td>Collaboration: Koichi Katoh</td>
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<td>Collaborators:</td>
<td>Junpei Kikunoki</td>
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**Potential COI of the participant**

- Potential COI of the marital partner, biological family members, or those who share income and property
- Potential COI of the head of the organization/department to which the participant belongs (when the participant is in the position of cooperative research with the head of the organization/department)
<table>
<thead>
<tr>
<th>Author</th>
<th>Employment/leadership position (private company)</th>
<th>Stakeholder</th>
<th>Patents</th>
<th>Honors</th>
<th>Payment for manuscript</th>
<th>Research grant</th>
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<th>Endowed chair</th>
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<td>Independent Assessment Committee</td>
<td>Hideaki Yoshino</td>
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<td>Takeda Pharmaceutical Company Limited</td>
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*Note that the corporation is omitted.*

No potential COI for the following members:

Members:
- Nobusada Funabashi
- Teruhito Mochizuki
- Masaru Miura

Collaborators:
- Yunits Ishikura
- Hiroshi Kameyama
- Teruhito Kido
- Akira Kurata
- Akihisa Kurata
- Akira Sato
- Mamoru Tezuka
- Takuya Nakahashi
- Akiyoshi Hashimoto
- Koichi Hiyama
- Masaaki Higashi
- Katsuo Yoshida
- Hitoshi Wada