Guidelines for Elective Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease (JCS 2011) Published in 2012

– Digest Version –

JCS Joint Working Group

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Abbreviations

AATS: American Association for Thoracic Surgery	JCIS: Japanese Coronary Intervention Study
ACC(F): American College of Cardiology (Foundation)	JCRAC: Joint Center for Researchers, Associates and Clinicians
ACE: angiotensin converting enzyme	JDS: Japan Diabetes Society
ACS: acute coronary syndrome	JSAP: Japanese Stable Angina Pectoris
ACT: activated coagulation time	K _{ATP} : ATP-sensitive potassium
AHA: American Heart Association	LAD: left anterior descending
ARB: angiotensin II receptor blocker	LDL: low density lipoprotein
ASNC: American Society of Nuclear Cardiology	LMT: left main coronary trunk
BARI 2D: Bypass Angioplasty Revascularization Investigation 2 Diabetes)	LVEF: left ventricular ejection fraction
BMI: body mass index	MACE: major adverse cardiovascular event
BMS: bare metal stent	MASS II: Medicine, Angioplasty, or Surgery Study
CAD: coronary artery disease	MDCT: multi-detector computed tomography
CAG: coronary angiography	MHLW: Ministry of Health, Labour and Welfare
CABG: coronary artery bypass grafting	NGSP: National Glycohemoglobin Standardization Program
CK: creatine kinase	NHI: National Health Insurance
COURAGE: Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation	PCI: percutaneous coronary intervention
CREDO-Kyoto: Coronary REvascularization Demonstrating Outcome Study in Kyoto	POBA: percutaneous old balloon angioplasty
CT: computed tomography	PTCA: percutaneous transluminal coronary angioplasty
DCA: directional coronary atherectomy	PTCRA: percutaneous transluminal coronary rotational ablation
DES: drug eluting stent	QOL: quality of life
EACTS: European Association for Cardiothoracic Surgery	SCAI: Society for Cardiovascular Angiography and Interventions
ECG: electrocardiography	SPECT: single photon emission computed tomography
ESC: European Society of Cardiology	STS: Society of Thoracic Surgeons
Hb: hemoglobin	SWISSI II: Swiss Interventional Study on Silent Ischemia Type II
HDL: high density lipoprotein	SYNTAX: SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery
IABP: intra-aortic balloon pump	TIMI: Thrombolysis In Myocardial Infarction
ITA: internal thoracic artery	
IVUS: intravascular ultrasound imaging	

Coronary Revascularization (PCI/CABG) for Stable Coronary Artery Disease: Statements and Indications Proposed by the Coronary Revascularization Council

I Statements

1. Purpose of Coronary Revascularization

In patients with stable coronary artery disease (CAD), coronary revascularization is performed to improve long-term prognosis, prevent myocardial infarction and unstable angina, and improve the quality of life (QOL) by reducing anginal symptoms.

2. Collaboration of Interventional Cardiologists and Cardiac Surgeons in Decision-Making Process for Coronary Revascularization

It is desirable that interventional cardiologists and cardiac surgeons discuss to decide how to perform coronary revascularization in patients with severe stable CAD (i.e., patients with left main disease, patients with multivessel disease involving the proximal left anterior descending [LAD] artery, especially patients with multivessel disease associated with cardiac dysfunction, and diabetic patients with multivessel disease) before proposing treatment options to the patients, and that the patients should decide their treatment options by themselves.

3. Treatment Outcomes of PCI

As compared with recent initial intensive medical therapy alone, percutaneous coronary intervention (PCI) plus medical therapy is effective in reducing anginal symptoms, but does not improve long-term prognosis or prevent myocardial infarction [**Level of Evidence: A**].

PCI plus medical therapy is not superior to recent initial intensive medical therapy in the prevention of unstable angina [**Level of Evidence: B**]. On the other hand, data available in Japan indicate the preventive effects of PCI plus medical therapy [**Level of Evidence: B**].

The incidence of repeat revascularization is lower in patients receiving drug eluting stent (DES) than those receiving percutaneous old balloon angioplasty (POBA) or bare metal stent (BMS) [**Level of Evidence: A**]. However, there is no conclusive evidence indicating that DES improves long-term prognosis and decreases the incidence of myocardial infarction.

4. Treatment Outcomes of CABG

Coronary artery bypass grafting (CABG) is effective in reducing anginal symptoms, prevents myocardial infarction, and improves long-term prognosis [**Level of Evidence: A**]. The use of internal thoracic artery (ITA) grafts increases and prolongs

the beneficial effects of CABG on long-term prognosis [**Level of Evidence: B**].

5. PCI and CABG for Patients With Multivessel Disease

In randomized clinical studies in patients with multivessel disease without left main involvement before the DES era, the incidence of repeat revascularization was higher in patients receiving PCI than those receiving CABG, but these methods did not differ in terms of long-term prognosis and incidence of myocardial infarction [**Level of Evidence: A**].

In recent comparative studies in the DES era, the long-term prognosis of patients with three-vessel disease without left main involvement is poorer in patients receiving PCI than in those undergoing CABG, and the incidences of myocardial infarction and repeat revascularization are also high in patients receiving PCI [**Level of Evidence: B**].

6. PCI and CABG for the Treatment of Unprotected Left Main Disease

Basically, patients with unprotected left main disease should be treated with CABG. However, no high-level evidence is available regarding comparisons between CABG and PCI in this patient population. In recent comparative studies in the DES era, the incidence of repeat revascularization was higher in patients receiving PCI than CABG for the treatment of left main disease, but no differences were observed in long-term prognosis and the incidence of myocardial infarction.

II Descriptions

1. Introduction

In 2000, the first guidelines for interventional therapy of CAD in Japan were published.¹ The interventional therapy described in the guideline included CABG, and recommended indications of elective interventions were described. In 2006, the Guidelines for the Clinical Application of Bypass Grafts and the Surgical Techniques (JCS 2006) were published,² and many other guideline documents were published to promote comprehensive treatment of ischemic heart disease, including primary prevention, diagnosis and understanding pathophysiology, treatment strategies, and secondary prevention.

During the ten years since the publication of the “Guidelines on Indications of Elective Intervention (including CABG) in the Treatment of Coronary Artery Disease¹”, techniques for coronary revascularization such as PCI and CABG have improved significantly. The Japanese Circulation Society started to revise the guideline documents to reflect the advancement of interventional techniques. During the revision process, a development of restructured guideline documents that systematically describe coronary revascularization and includes the “Guidelines for the Clinical Application of Bypass Grafts and the Surgical Techniques (JCS 2006)” was proposed.² A consensus was achieved that the new comprehensive guideline documents will consist of general statements including basic principles of coronary revascularization such as the merits and demerits of different techniques, a multifaceted comparison between PCI and CABG, and the criteria for selecting between PCI and CABG, and specific guideline documents describing practical matters. The general statements will be consistent with the “Guidelines for Elective Percutaneous Coronary Intervention in Patients with Stable Coronary Disease (JCS 2011)”, which is a revision of the PCI guidelines published in 2000,¹ and the “Guidelines for the Clinical Application of Bypass Grafts and the Surgical Techniques (JCS 2011)”, which is a

revision of the CABG guidelines published in 2006.² The present guideline documents discuss stable CAD, and do not include acute-phase CAD.

The joint guidelines on coronary revascularization prepared by the European Society of Cardiology (ESC) and the European Association for Cardiothoracic Surgery (EACTS) in 2010 emphasize the importance of the heart team including general practitioners, interventional cardiologists and cardiac surgeons in the treatment of CAD.³ It is expected that the heart team will play a central role in the treatment of CAD in Japan. To better describe the roles of the heart team, the statements, descriptions, and indications for coronary revascularization in the general statements chapter of the revised PCI and CABG guideline documents were prepared through extensive discussion by the “Coronary Revascularization Council” consisting of interventional cardiologists, cardiac surgeons and diabetes specialists who represent the Japanese Circulation Society, the Japanese College of Cardiology, the Japanese Coronary Association, the Japanese Association of Cardiovascular Intervention and Therapeutics, the Japanese Society for Cardiovascular Surgery, the Japanese Association for Thoracic Surgery, the Japanese Association for Coronary Artery Surgery, and the Japan Diabetes Society.

2. Criteria for Selection of Evidence, Levels of Evidence, Interpretation of Study Results, and Classification of Recommendations

Because these statements represent the basis of guidelines, the statements and descriptions were prepared on the basis only of high-level evidence (**Level A**, evidence demonstrated with more than one randomized clinical studies or meta-analyses, and **Level B**, demonstrated with a randomized clinical study or multicenter, large-scale registry studies). However, as the SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) study (www.syntaxscore.com) is the only randomized clinical study that directly compared CABG vs. PCI using DES, the results of sub-analyses, which were **Level C** evidence, were also used. **Level C** evidence represents consensus opinion of experts, small-scale clinical studies, results of sub-analysis, and others.

Classification of Recommendations

Class I: There is evidence and/or general agreement that a given procedure/treatment is useful/effective.

Class II: There is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a given procedure/treatment.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: There is evidence and/or general agreement that the procedure/treatment is not useful/effective, and in some cases may be harmful.

Although the true treatment outcome can be assessed in randomized clinical studies, it is difficult to assess the validity of indications and treatment outcomes of PCI and CABG in the actual clinical practice by using the results of randomized clinical studies and meta-analyses only. We thus placed emphasis on the results of multicenter, large-scale registry studies. It has been widely known that the clinical characteristics, treatment strategies and outcomes of patients with stable CAD in Japan differ from those in Western countries, but much of high-level evidence available is on the Western patient populations. We

should create patient database of PCI and CABG and assess the data to establish evidence in patients in Japan.

3. Purpose of Coronary Revascularization: Statement #1

The most important purpose of coronary revascularization for stable CAD is to improve long-term prognosis by preventing the incidence of myocardial infarction and unstable angina. Because stable CAD may often manifest as angina, management of angina to improve QOL is also an important purpose.

4. The Importance of Collaboration Between Interventional Cardiologists and Cardiac Surgeons in Decision-Making Process for Coronary Revascularization: Statement #2

PCI and CABG, two different approaches sharing a common goal of ensuring successful coronary revascularization, have different risks and benefits. When physicians consider whether PCI or CABG is better for a given patient, they should assess the expected outcomes of each technique on the patient as well as the risk of complications (e.g., stroke, infections, contrast-induced nephropathy, and radiation exposure), the safety and invasiveness of the technique used, expected duration of hospitalization, medical cost, and underlying diseases to determine the optimal treatment strategy for the patients.

Especially in patients of severe stable CAD (i.e., patients with left main disease, patients with multivessel disease involving the proximal LAD artery, especially patients with multivessel disease associated with cardiac dysfunction, and diabetic patients with multivessel disease), interventional cardiologists and cardiac surgeons should discuss to determine treatment options, and should fully inform patients about the expected short- and long-term treatment outcomes of PCI and CABG, the safety and invasiveness of these techniques, and the possibility of requiring further treatment before obtaining informed consent. When the heart team, a multidisciplinary team of healthcare professionals including interventional cardiologists and cardiac surgeons, is difficult to establish in the hospital due to the unavailability of cardiac surgeons, it is desirable to collaborate with nearby hospitals providing cardiac surgery services to ensure the safe treatment. Because the treatment outcomes of PCI and CABG may largely depend on the skill and expertise of interventionists/surgeons and medical team members, physicians should consider these factors carefully to determine what is the optimal treatment strategy for each patient. Data on the results in individual institutions such as the number of patients treated, severity of CAD, and short- and long-term outcomes should be accumulated and analyzed in a formal framework.

5. Treatment Outcomes of PCI: Statement #3

A meta-analysis of 11 randomized clinical studies of PCI in a total of 2,950 patients with stable CAD revealed that PCI does not improve long-term prognosis or prevent myocardial infarction as compared with patients receiving initial medical therapy.⁴ In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), a randomized clinical study in 2,287 patients with stable angina (excluding patients with left main disease; proximal LAD disease was present in 31%, one-vessel disease in 31%, two-vessel disease in 39%, three-vessel disease in 30%, and diabetes in 32%), patients were randomized to receive PCI with optimal medical therapy (PCI plus medical therapy group) or to start optimal medical therapy and receive PCI whenever necessary (initial intensive medical therapy group).⁵ All patients received optimal medical therapy during the study (treatment targets were (1) smoking cessation, (2) low density lipoprotein [LDL] lev-

els of 60 to 85 mg/dL, (3) high density lipoprotein [HDL] level of ≥ 40 mg/dL, (4) triglyceride of < 150 mg/dL, 30 to 45 minutes of moderate exercise 5 times per week, body mass index [BMI] of < 25 kg/m², blood pressure of $< 130/85$ mmHg, and hemoglobin A1c [HbA1c] [National Glycohemoglobin Standardization Program; NGSP value]* of $< 7.0\%$). During the follow-up period for 4.6 years, there were no differences between the two groups in the incidences of death, myocardial infarction and unstable angina. In the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes), a randomized clinical study in 1,605 patients with type 2 diabetes (excluding patients with left main disease; proximal LAD disease was present in 10.3%, and three-vessel disease in 20.3%; the prevalences of one- and two-vessel disease were not reported), there were no significant differences in the incidences of death and myocardial infarction during the 5.3-year follow-up period between patients receiving PCI plus medical therapy and patients receiving initial intensive medical therapy and undergoing PCI whenever necessary.^{6,7} All patients received initial intensive medical therapy during the study (treatment targets were HbA1c [NGSP value] of $< 7.0\%$, LDL level of < 100 mg/dL, and blood pressure of $< 130/80$ mmHg). The reasons why PCI plus medical therapy did not improve the incidences of death and myocardial infarction may include the following: (1) Because unstable plaques, a major cause of acute coronary syndrome (ACS), are often present in nonsignificant stenotic lesions, while significant stenoses causing anginal symptoms are often related to stable plaques, treatment of significant stenoses by PCI did not affect the incidences of myocardial infarction and death; (2) The incidence of cardiac accidents in patients receiving initial intensive medical therapy was lower than expected in both the COURAGE and BARI 2D studies, and these results are considered to reflect favorable efficacy of systemic treatment with aggressive risk management strategies. (3) Among patients receiving initial intensive medical therapy, patients with severe myocardial ischemia not responding to medical therapy, which accounted for 30 to 40%, underwent PCI for culprit lesions and showed an improvement in myocardial ischemia. As mentioned in the item (3) above, about one in three patients receiving initial intensive medical therapy underwent PCI. This means that these studies compared a group of patients undergoing PCI at the initiation of the study and a group of patients among whom PCI was conducted for selected patients whenever necessary. The absence of differences between the PCI plus medical therapy group and the initial intensive medical therapy group does not lead the conclusion that PCI does not improve long-term prognosis or prevent myocardial infarction. In order to demonstrate the effects of PCI on the incidences of death and myocardial infarction in clinical studies, patients not responding to medical therapy should be followed up for a long period of time without conducting PCI, but such studies are not allowed for ethical reasons.

*In Japan, HbA1c has been encouraged to report as the NGSP value rather than the conventional JDS (Japan Diabetes Society) value from April 1, 2012, onward. The relationship between the NGSP and the conventional JDS is as follows: NGSP value (%) = $1.02 \times \text{JDS value} (\%) + 0.25\%$. Within the clinically relevant range between 5.0 to 9.9% (JDS), the relationship may be expressed as follows: HbA1c (NGSP) = HbA1c (JDS) + 0.4%.

In the COURAGE study, patients in the PCI plus medical therapy group showed less anginal symptoms and better QOL

as compared with those in the initial intensive medical therapy group, but these differences disappeared in the second to third year of the study.⁸ These findings may be explained by the study design where in the initial intensive medical therapy group patients not responding to medical therapy underwent PCI.

In the JSAP (Japanese Stable Angina Pectoris), a randomized clinical study in 384 low-risk patients with stable angina (one-vessel disease was present in 67.5%, two-vessel disease in 38.5%, and diabetes in 39.6%; patients with left main disease, those with three-vessel diseases, and those with proximal LAD disease were excluded), patients undergoing PCI plus medical therapy did not appear to be superior to patients with initial medical therapy (at the discretion of the treating physicians) in terms of the incidences of death and myocardial infarction during the 3.2-year follow-up period.⁹ In contrast to the COURAGE study, the JSAP study demonstrated that PCI plus medical therapy prevented the development of unstable angina and reduced anginal symptoms, and the differences were observed even in the third year of the study. Although the two studies cannot be compared directly as they are substantially different in terms of patient characteristics and drug treatment, the difference between the results of the COURAGE and JSAP studies may be explained with the following two facts. (1) While an aggressive intervention for multiple risk factors was made in the COURAGE study, in the JSAP study drug treatment such as statin therapy during the follow-up period was performed at the discretion of treating physicians. (2) The incidence of ACS developing as an acute complication of PCI may be lower among patients in Japan than among Western patients.

The results of meta-analyses revealed that the incidence of revascularization was significantly lower in patients receiving DES than BMS, indicating that DES is effective in the prevention of restenosis.^{10,11} However, although the restenosis rate has been decreasing as PCI devices become more advanced from POBA, BMS to DES, the incidences of death and myocardial infarction among patients receiving coronary revascularization have not improved.^{10,11} The absence of improvement is thought to be a result of the following facts: (1) Because repeat PCI for restenosis is easily and frequently performed, the advancement of stents used in PCI has little influence on the severity of myocardial ischemia after repeat PCI; and (2) PCI has been indicated for severer CAD as PCI devices become more advanced.

6. Treatment Outcomes of CABG: Statement #4

In a systematic overview using individual patient data from 7 randomized clinical studies in a total of 2,649 patients with stable CAD (among whom left main disease was present in 6.6%, proximal LAD disease in 59.4%, one-vessel disease in 10.2%, two-vessel disease in 32.4%, and three-vessel disease in 50.6%, and diabetes in 9.6%), Yusuf et al. reported in 1994 that the initial CABG group had significantly lower risk of death than the initial medical treatment group (37.4% of patients underwent CABG during the study period), and demonstrated that CABG is effective in improving long-term prognosis.¹² The improvement in long-term prognosis became apparent at 5 years, and also observed at 10 years. A sub-analysis revealed that the risk reduction was greater in patients with proximal LAD disease, those with three-vessel disease, those with left main disease, and those with cardiac dysfunction, and the risk reduction was highest in patients with left main disease. Initial CABG was not effective in this regard for patients with one- or two-vessel diseases.

The ITAs are considered “the gold standard” of CABG grafts

because of the favorable long-term graft patency. In a large multicenter registry in the United States, ITA grafts conferred a survival advantage as compared with vein grafts.¹³ The survival curves of the two groups showed separation over the years of follow-up, with a more marked downsloping after 8 years and thereafter during the follow-up period (mean, 16.8 years). In a meta-analysis of observational studies, Taggart et al. reported that bilateral ITA grafts give better survival rates than single ITA grafts.¹⁴

Yusuf et al. analyzed the results of randomized clinical studies conducted in 1972 and 1984, which do not reflect the current surgical procedures and drug regimens.¹² The readers should be aware that (1) the 30-day mortality of patients undergoing CABG was 3.2%, which was higher than those in recent studies; (2) the use of ITA grafts, which are known to improve long-term prognosis, was limited to <10% of patients; and (3) patients did not receive statins, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) that are commonly administered to patients undergoing CABG.

In the BARI 2D study recently conducted in 763 patients with type 2 diabetes (proximal LAD disease was present in 19.4%, and three-vessel disease in 52.4%; the prevalences of one- and two-vessel diseases were not reported), at 5-year follow-up, incidence of death did not differ significantly between the CABG and the initial intensive medical therapy group (39.7% of the patients underwent coronary revascularization during the study).⁶ In the MASS II (Medicine, Angioplasty, or Surgery Study), a randomized clinical study in 611 patients with multivessel disease (not including patients with left main disease and patients with cardiac dysfunction), the overall mortality and incidence of cardiac death at the 5-year follow-up did not differ significantly between the CABG group and the medical therapy group (39.4% of the patients underwent coronary revascularization during the study).¹⁵ However, the incidence of cardiac death at the 10-year follow-up was significantly lower in the CABG group than the medical therapy group, although the overall mortality did not differ between the two groups.¹⁶ At the present time when intensive medical therapy is available, the beneficial effect of CABG on long-term prognosis may have become smaller than before, or longer follow-up is required to demonstrate a significant difference between CABG and intensive medical therapy. Randomized clinical studies for at least 10 years should be performed to determine the true beneficial effects of CABG on long-term prognosis and how long such effect will continue.

The results of the BARI 2D study indicated that CABG was superior to initial intensive medical therapy in terms of the prevention of myocardial infarction⁷ and QOL including activity status.¹⁷ In the MASS II, the incidence of myocardial infarction at 10-year follow-up was lower in the CABG group than in the medical therapy group.¹⁶ The mechanism of the prevention of acute myocardial infarction in patients receiving CABG is thought to be “distal protection” in which bypass grafts may protect myocardium distal to a ruptured plaque when a graft is connected to the distal part of the clogged artery.¹⁸ During the 10-year follow-up in the MASS II, patients in the CABG group showed a greater improvement in anginal symptoms than the initial medical therapy group.¹⁶

7. Important Points to Be Considered When Interpreting the Results of Randomized Clinical Studies Comparing PCI and CABG

A large number of randomized clinical studies have been conducted to compare PCI and CABG. Physicians should con-

sider the following three points when interpreting the results of such studies. First, because patients with left main disease or three-vessel disease have been historically considered to require CABG, patients with left main disease have been excluded in the majority of randomized clinical studies, and the percentage of patients with three-vessel disease has been small. These studies have been conducted in patients with coronary stenosis treatable with PCI, and patients with complex lesions that require CABG rather than PCI have not been enrolled in these studies. Second, it is believed that 5 to 10 years of follow-up is required to confirm the treatment outcomes of CABG over PCI, but the observation period is often too short in many studies. Third, the importance of intensive medical therapy is widely acknowledged, but drug regimens during the follow-up period differ between the PCI and CABG groups.

The SYNTAX, the only randomized clinical study to date that directly compared between CABG and PCI with DES, was intended to show non-inferiority of PCI compared with CABG in 1,800 patients with left main disease or three-vessel disease (left main disease was present in 39%, three-vessel disease in 61%, and diabetes in 25%). For the primary endpoint, the 12-month rate of major adverse cardiac or cerebrovascular events (i.e., death, stroke, myocardial infarction, or repeat revascularization), were significantly higher in the PCI group, so the non-inferiority of PCI as compared with CABG was not demonstrated.¹⁹ At 3-year follow-up, the incidences of death (CABG 6.7% vs. PCI 8.6%) and stroke (CABG 3.4% vs. PCI 2.0%) were not significantly different between the treatment groups. However, the incidences of myocardial infarction (CABG 3.6% vs. PCI 7.1%) and repeat revascularization (CABG 10.7% vs. PCI 19.7%) were higher in PCI-treated patients.²⁰ It should be noted that among 3,075 patients registered in the SYNTAX study, 1,800 patients (59%) were considered to be indicated for both PCI and CABG and were randomly assigned to undergo CABG or PCI with DES, while the remaining 1,275 patients were enrolled in the registry study because 84% of them (1,077 patients) were indicated only for CABG, and 16% of them (198 patients) were indicated only for PCI. The most common reasons for the enrollment in the CABG registry were complex lesions inaccessible to PCI (70.9%) and chronic total occlusion (22.0%), while those in the PCI registry were underlying diseases (70.7%) and unavailability of suitable grafts (9.1%). Patients in the randomized cohort will continue to be followed for 5 years. Patients in the CABG cohort were less likely to receive antiplatelet drugs, statins, β -blockers, ARBs, and calcium channel blockers than those in PCI cohort.

8. PCI and CABG for Patients With Multivessel Disease: Statement #5

Hlatky et al. conducted a collaborative analysis of data from 10 randomized trials comparing between CABG and PCI not using DES which provided data on 7,812 patients (proximal LAD disease was present in 51%, two-vessel disease in 63%, three-vessel disease in 37%, and diabetes in 16%), and reported that the incidence of repeat revascularization during the 6-year follow-up period was higher in patients receiving PCI than CABG, but the incidences of death and myocardial infarction did not differ significantly between the two groups.²¹ However, a sub-analysis of the SYNTAX study revealed incidences of death, myocardial infarction and repeat revascularization in patients with three-vessel disease were lower in patients undergoing CABG than those receiving PCI with DES. When patients with three-vessel disease were further classified into those with higher and lower SYNTAX scores, those with

lower SYNTAX scores showed no significant differences in incidences of death, myocardial infarction and stroke between PCI and CABG, while those with higher SYNTAX scores showed superiority of CABG in these measures. According to these data, the ESC/EACTS Guidelines on Myocardial Revascularization published in August 2010,³ CABG is a **Class I** recommendation with **Level of Evidence: A** for patients with three-vessel disease, and PCI is a **Class IIa** recommendation for patients with three-vessel disease and a SYNTAX score of ≤ 22 , and a **Class III** recommendation for patients with complex three-vessel disease and a SYNTAX score of ≥ 23 .

Observational studies such as the CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome Study in Kyoto) PCI/CABG registry in Japan²² and a registry study in New York State²³ have compared PCI and CABG in the treatment of multivessel disease without left main involvement in the clinical setting. In the CREDO-Kyoto registry in 5,420 patients (proximal LAD disease was present in 80%, two-vessel disease in 49%, three-vessel disease in 51%, diabetes in 46%, and total occlusion in 40%), the risk-adjusted mortality tended to be higher in PCI without DES than CABG, and significantly higher in PCI than CABG in diabetic patients and patients with cardiac dysfunction. However, there were no differences between PCI and CABG when compared in patients <75 years of age. In the New York State registry study in 17,400 patients (proximal LAD disease was present in 52%, two-vessel disease in 56%, three-vessel disease in 41%, and diabetes in 38%), the incidence of repeat revascularization, risk-adjusted incidence of myocardial infarction, and mortality were lower in CABG than PCI with DES. The incidences of death and myocardial infarction were lower in CABG than PCI in patients with two- or three-vessel disease group, elderly patients ≥ 80 years of age, and patients with cardiac dysfunction. In an analysis of 6,327 patients with multivessel and/or left main disease in the CREDO-Kyoto registry, the risk-adjusted mortality and incidences of myocardial infarction and repeat revascularization during the 3.5-year follow-up period were higher in patients after PCI than those after CABG.²⁴ Mortality was also higher in PCI than CABG in patients with diabetes, patients with cardiac dysfunction, patients with proximal LAD disease, and elderly patients ≥ 75 years of age. The incidence of stroke was lower in PCI than CABG, but did not differ between PCI and off-pump CABG.

9. PCI and CABG for Patients With Left Main Disease: Statement #6

In a systemic overview of individual patient data from 7 randomized clinical studies, Yusuf et al. reported that the reduction in risk of death by CABG as compared with medical therapy was greatest in patients with left main disease.¹² Recent studies of stents vs. CABG for left main disease suggested that PCI might be an acceptable treatment option for patients with left main disease.²⁵ However, these studies included patients with stable CAD and patients with ACS. To date, there have been no well-conducted observational studies or randomized clinical studies that compared between PCI and CABG for the treatment of unprotected left main lesions in patients with stable CAD. Accordingly, CABG rather than PCI has been selected in coronary revascularization for patients with left main disease.

In the ACCF/SCAI/STS/AATS/AHA/ASNC (American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions/Society of Thoracic Surgeons/American Association for Thoracic Surgery/American Heart Association/ American Society of Nuclear Cardiology) 2009

Appropriateness Criteria for Coronary Revascularization, CABG is considered as an appropriate procedure for unprotected left main disease, while PCI is considered inappropriate even for isolated left main lesions.²⁶ The 2009 Focused Updates of the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention describe recommendations for PCI for unprotected left main disease as follows:²⁷ PCI of the left main coronary artery with stents as an alternative to CABG may be considered in patients with anatomic conditions that are associated with a low risk of PCI procedural complications (i.e., isolated left main lesions or left main plus one-vessel disease) and risk factors such as severe lung disease, prior thoracic surgery, or poor bypass graft targets that would make CABG a high-risk procedure or unlikely to be successful. Conversely, CABG for unprotected left main disease may be relatively more favorable for patients with left main plus multivessel disease, distal/bifurcation left main lesions, or low surgical risk with a good chance of technical success.²⁷ In the j-Cypher registry, a multicenter large-scale registry of patients undergoing sirolimus-eluting stent implantation in Japan, among patients with bifurcation lesions who underwent PCI for unprotected left main disease, patients with stenting of both the main and side branches using two-stent strategy had significantly higher incidences of cardiac death and revascularization than those with main-branch stenting alone using one-stent strategy.²⁸

The results of a sub-analysis of SYNTAX study after 3-year follow-up, the incidence of repeat revascularization was lower in patients undergoing CABG than those receiving PCI with DES, although the incidences of death and myocardial infarction did not differ between the two groups.²⁰ Among patients with left main disease and lower SYNTAX scores, there were no differences in incidences of death, myocardial infarction and stroke between the PCI with DES and CABG groups, while among those with higher SYNTAX scores, incidences of death and myocardial infarction tended to be lower in CABG than PCI with DES groups. However, we should be aware of the limitations of randomized clinical studies. In the SYNTAX study, 312 (29%) of the 1,085 patients with left main disease who were enrolled in the study were considered to be indicated only for CABG, and were enrolled in the registry study. In August 2010, the ESC and the EACTS published joint guidelines on myocardial revascularization. In the ESC/EACTS

joint guidelines, CABG is a **Class I** recommendation with **Level of Evidence: A** for patients with left main disease on the basis of the results of the SYNTAX study.³ PCI is a **Class IIa** or **IIb** recommendation with **Level of Evidence: B** for patients with isolated ostial or shaft lesions of the left main coronary artery or patients with left main plus one-vessel disease, and is a **Class IIb** or **III** recommendation for the treatment of bifurcation lesions in patients with isolated left main coronary artery/left main plus one-vessel disease or the treatment of left main plus multivessel disease.

III Indications for Coronary Revascularization (PCI/CABG) in Patients With Stable Coronary Artery Disease (Table 1)

1. Lifestyle intervention and drug treatment are essential components of the treatment of stable CAD. Coronary revascularization should be performed for patients in whom the improvement of physical conditions and long-term prognosis are expected.
2. Patients with one- or two-vessel disease without proximal LAD involvement are indicated for PCI. Both PCI and CABG should be considered for patients with one- or two-vessel disease with proximal LAD involvement. CABG should be considered for patients with ostial LAD lesions.
3. Patients with three-vessel disease should be treated with CABG, in principle, but may be treated with PCI when they have risk factors that would make CABG a high-risk procedure, or when PCI is considered to be a safe procedure because of the absence of proximal LAD lesions or other lesions.
4. Basically, patients with unprotected left main disease should be treated with CABG, but PCI may be alternative to CABG when they have risk factors that would make CABG a high-risk procedure, or when PCI is considered to be a safe procedure because of targeting ostial/shaft lesions of left main trunk (LMT) or other lesions. PCI must be conducted in a condition where emergency CABG can be performed without delay.

The above indications are provided as basic principles. Treatment strategies for individual patients should be determined on the basis of their clinical and anatomical characteristics, the

Table 1. Indications of PCI and CABG

Anatomical conditions	PCI	CABG
1- or 2-vessel disease		
No proximal LAD lesions	I A	IIb C
Proximal LAD lesions (without ostial LAD lesions)	I C	I A
Ostial LAD lesions	IIb C	I A
3-vessel disease		
No proximal LAD lesions	IIb B	I A
Proximal LAD lesions	III B	I A
Unprotected left main disease		
Isolated ostial or shaft lesions plus 1-vessel disease	IIb C	I A
Isolated bifurcation lesions or bifurcation lesions plus 1-vessel disease	III C / IIb C*	I A
Multivessel disease	III C	I A

*IIb recommendation for patients with no lesions involving the ostium of the circumflex artery for whom the use of PCI has been approved by the heart team including cardiac surgeons.
CABG, coronary artery bypass grafting; LAD, left anterior descending coronary artery; PCI, percutaneous coronary intervention.

results and systems available in each institution, the long-term treatment goals, and others. Especially for patients with severe CAD, interventional cardiologists and cardiac surgeons should discuss and decide optimal treatment options to be proposed

to the patients.

A PCI/CABG registry must be established as soon as possible to prepare for the revision of the guideline documents on the basis of clinical evidence in Japan.

Introduction of the Revised Guidelines

Revascularization techniques including PCI and CABG for the treatment of CAD are performed as elective interventions for the treatment of stable CAD or emergency interventions for the treatment of ACS. Since the publication of the “Guidelines for Indications of Elective Intervention (including CABG) in the Treatment of Coronary Artery Disease (Chair: Hisayoshi Fujiwara)” by the Joint Working Groups of eight societies including the Japanese Circulation Society in 2000,¹ 11 years have passed and techniques of PCI and CABG have advanced significantly. We decided to revise the previous guideline documents totally in order to reflect the current practices of revascularization.

The revised guideline documents consist of two parts. The first part entitled “Coronary Revascularization (PCI/CABG) for Stable Coronary Artery Disease: Statements and Indications Proposed by the Coronary Revascularization Council”, which is the common general statement of the two revised PCI/CABG guideline documents, was prepared through extensive discussion by the Coronary Revascularization Council consisting of interventional cardiologists, cardiac surgeons and diabetes specialists who represent the Japanese Circulation Society, the Japanese College of Cardiology, the Japanese Coronary Association, the Japanese Society for Cardiovascular Surgery, the Japanese Association of Cardiovascular Intervention and Therapeutics, the Japanese Association for Thoracic Surgery, the Japanese Association for Coronary Artery Surgery, and the Japan Diabetes Society. The first part was followed by the revision of two specific guideline documents, i.e., the “Guidelines for Elective Percutaneous Coronary Intervention in Patients with Stable Coronary Disease (JCS 2011)”, which is totally-revised edition of guidelines published in 2000,¹ and the “Guidelines for the Clinical Application of Bypass Grafts and the Surgical Techniques (JCS 2011)²⁹”, which is partly-revised edition of the previous guidelines published in 2006.² The second parts were prepared by the above-mentioned societies to ensure consistency with the first part.

We totally revised previous guideline documents for the following four reasons:

1. The Advancement in Revascularization Techniques Especially PCI Procedures and Expanded Indications

During the 11 years since the publication of the “Guidelines

for Indications of Elective Intervention (including CABG) in the Treatment of Coronary Artery Disease¹”, it has been demonstrated that intensive medical therapy using statins and other drugs to prevent the progression of atherosclerosis and induce the regression of plaques may promote the regression of coronary atherosclerotic lesions and decrease major adverse cardiovascular events (MACE), and the use of ITA grafts in CABG has become prevalent and improved prognosis further. However, the most prominent changes are the advancement of PCI techniques and expanded indications.

2. The Advancement of the Heart Team in Selecting Treatment Options

3. The Need for Classification of Recommendations and Level of Evidence

Recommendations are described with classification of recommendations in terms of efficacy/usefulness of procedures and treatment, and level of evidence, which were not indicated in the previous guideline documents.

4. Changes in the Purpose and Social Roles of the Guidelines

Reflecting on current medical setting in Japan, the commentary on modifications of the National Health Insurance (NHI) price list in 2010 describes that physicians should provide NHI-based medical practice according to the guidelines published by academic societies. Regarding elective PCI, the commentary describes³⁰ that health care costs for elective PCI will be covered by the NHI only when the procedures are conducted according to the “Guidelines on Indications of Elective Intervention (including CABG) in the Treatment of Coronary Disease (the previous guidelines published in 2000)¹”.

On the basis of the changes in 11 years described as above, the present guideline documents were prepared to provide recommendations that may play a social role and reflect the current situation and specific circumstances in Japan according to the up-to-date PCI techniques and current evidence in and outside Japan.

I Current Practice of PCI in Japan

1. Background

- In Japan, mortality due to cerebrovascular diseases peaked in 1965 and has decreased substantially over time since then.
- Mortality due to cardiac disease has remained steady for 40 years. The incidence of CAD has not changed significantly from 1960s to 2000.
- Mortality due to CAD in Japan is the lowest among devel-

oped countries, which is one-eighth to one-tenth of that in Eastern and Northern Europe and one-fifth in that in Western Europe and North America.³¹

Incidence of myocardial infarction (per 1,000 person-years).³²

Hisayama-cho: Male 1.6, female 0.7

Framingham Study: Male 7.1, female 4.2

- Recurrence rate of CAD among patients with a history of CAD is similar to that in Western countries.
- The number of individuals with coronary risk factors has been

increasing.

2. History and Current Status of PCI

- PCI was originally referred to as percutaneous transluminal coronary angioplasty (PTCA). In 1977, the world's first case of PTCA was balloon dilatation of coronary stenosis in Switzerland.
- Advancement of devices: After the establishment of POBA, directional coronary atherectomy (DCA), percutaneous transluminal coronary rotational ablation (PTCRA, Rotablator) and stenting were developed in 1990s, and DES became available in 2000s. Because of its usability and efficacy, DES has played a central role in PCI.
- The initial success rate of PCI increased from 70~80% (in 1980s) to 90~95% (in 1990s).
- The restenosis rate decreased over time: 40~50% for POBA, about 20% for BMS, and ≤10% for DES.
- Indications of PCI have expanded over time, and are used for the treatment of diffuse lesions, multivessel diseases, small vessel diseases, chronic occlusive lesions, in-stent restenosis, and LMT lesions.

3. Statistics on PCI

- No all-case surveillance has been conducted for PCI in Japan.

- In 2000, the JCIS (Japanese Coronary Intervention Study; supported by a Health and Labour Sciences Research Grant [Clinical Research for Evidence Based Medicine] from the Ministry of Health, Labour and Welfare [MHLW]) was in 8,268 institutions revealed that a total of 543,046 cases of coronary angiography (CAG) were conducted in Japan.³³ The prevalence is 1.4 times that in the United States.

PCI/CABG=146,992 procedures/23,584 procedures=6.23 times

Institutions conducting >100 cases/year of PCI accounted for 40.2% of the institutions

- Data in 2009 recorded in the JCRAC (Joint Center for Researchers, Associates and Clinicians) Data Center³⁴

CAG: 464,817 cases in 1,135 institutions

Emergency PCI: 59,072 cases in 1,039 institutions

Elective PCI: 160,824 cases in 1,067 institutions

- In Japan, the PCI/CABG ratio is high, and the number of PCI cases per institution is smaller than other developed countries. The benefits of centralized cardiac services that are common in some countries have been advocated as a measure to increase the number of cases per institution, but the availability of high-quality coronary angioplasty in many institutions throughout Japan may have significant benefits for people in Japan. The availability of PCI services in many local institutions may help reduce the time lag between the onset of ACS and the treatment, which may be a reason for the excellent treatment outcome in ACS in Japan than other countries.

II Assessment of the Results of Elective PCI in Japan

1. Background

Although an analysis of a total of 4,834 cases was conducted as research supported by Health and Labour Sciences Research Grant from the MHLW in 1997, and the results of CREDO-Kyoto PCI/CABG registry³⁵ were recently published, to date there has been no national registry data in Japan.

2. Definitions of PCI Success³⁶

- a) "Angiographic success": The consensus definition prior to

the widespread use of stents was the achievement of a minimum stenosis diameter reduction by ≥20% (before procedure) to <50% (after procedure) in the presence of grade 3 TIMI (Thrombolysis In Myocardial Infarction) flow without myocardial ischemia. Currently, with the use of stents, angiographic success is defined as a minimum stenosis diameter reduction to <20%. Angiographic success is achieved in ≥95% of patients with Type A lesions.

- b) "Procedural success" is defined as angiographic success without PCI-related complications.
- c) "Clinical success" is defined as the absence of myocardial ischemia for ≥6 months.

Table 2. Comparison of Drug Treatment for Stable Coronary Artery Disease in Western Countries (the COURAGE Study) and Japan (the JSAP Study and the CREDO-Kyoto Registry)

	COURAGE (%) ⁵	JSAP (%) ⁹	CREDO-Kyoto (%) ³⁵
Aspirin or other antiplatelet drugs	100	92	89
Long-acting calcium channel blockers	42	58	60
β-blockers	87	48	22
Long-acting nitrates	67	54	72
ACE inhibitors	59	18	27
ARBs	5	23	16
Satins	88	47	33
K _{ATP} channel openers	N/A	24	20*

*Based on personal communications.

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; CREDO-Kyoto, Coronary REvascularization Demonstrating Outcome Study in Kyoto; JSAP, Japanese Stable Angina Pectoris; K_{ATP}, ATP-sensitive potassium; N/A, not available.

3. Complications and Restenosis

- Procedural complications include death, acute myocardial infarction, cerebrovascular disorder, emergency surgery, puncture site bleeding (hematoma formation), pseudoaneurysm formation, renal dysfunction, peripheral arterial ischemia, and others. With the widespread use of DES, the risk of subacute stent thrombosis and late stent thrombosis is also concerned.³⁷
- The incidence of procedural complications has decreased over time. [Level of Evidence: A]
The United States:³⁸ Death in 0 to 1.1%, Q-wave acute myocardial infarction in 0.2 to 1.3%, emergency CABG in 0 to 1.9%, and subacute stent thrombosis in 0.2 to 3.9%.
Japan: Death in 0.05% to 0.2%, Q-wave acute myocardial infarction in 0.27 to 0.38%, and major complications including emergency CABG in 0.38 to 0.71%.
- Restenosis: In general, restenosis rate is affected by the patho-

physiology of coronary artery lesions, underlying conditions such as diabetes and chronic maintenance hemodialysis, among many other factors. The restenosis rate decreases when the residual stenosis is minimal ("the bigger the better" hypothesis).³⁹

4. Lifestyle Intervention and Drug Treatment

Treatment with antianginal drugs and drugs known to improve long-term prognosis, and management of risk factors such as smoking, hypertension, diabetes, dyslipidemia, and insufficient exercise are essential. However, physicians should be aware of the substantial differences in treatment strategies between Japan and Western countries: For example, treatment with long-acting calcium channel blockers, ATP-sensitive potassium (K_{ATP}) channel openers and ARBs are common in Japan, while β -blockers and ACE inhibitors are often used in Western countries (Table 2).^{5,9,35}

III Criteria for Institutions and Physicians Providing PCI in Japan

1. Background

- In Japan, small institutions conducting ≤ 200 PCI cases annually account for about 80% of the institutions providing PCI services. This percentage is higher than Western countries.³³
- In-house cardiac surgery is not available in 53% of institutions providing PCI services.
- There is no evidence indicating that the annual rate of major cardiac accidents (deaths in hospital, emergency repeat revascularization, and Q-wave acute myocardial infarction) among patients undergoing elective PCI is lower in smaller institutions.
- The criteria for institutions and physicians providing PCI in Japan differ substantially from those in Western countries.

2. Criteria Specified by the MHLW for Institutions Providing PCI

1. Criteria for Institutions Providing PTCA (PCI; Percutaneous Coronary Angioplasty, Percutaneous Coronary Thrombectomy, and Percutaneous Coronary Stenting) (Notification No. 86 of the Medical Economics Division of the Health Insurance Bureau Dated May 22, 2000)⁴⁰
 - (1) Medical institutions must have a minimum of one physician who has provided cardiovascular practice for at least 5 years.

- (2) Medical institutions must have notified the prefectural government office to provide medical services of cardiovascular surgery, and have a minimum of one full-time physician who has provided cardiovascular surgery practice for at least 5 years; provided, however, that this shall not apply to cases where there is necessary and close collaboration with other medical institutions that have notified the prefectural government office to provide medical services of the cardiovascular surgery, have a minimum of one full-time physician who has provided cardiovascular surgery practice for at least 5 years, and are able to provide emergency services.

2. Criteria for Institutions Providing Percutaneous Coronary Angioplasty Using PTCRA (Rotablator) (Notification No. 0305-3 of the Medical Economics Division of the Health Insurance Bureau dated March 5, 2010)⁴¹

- (1) Medical institutions must have notified the prefectural government office to provide medical services of cardiology and cardiovascular surgery.
- (2) Medical institutions must have performed a minimum of 30 cases of open-heart surgery, coronary or aortic bypass surgery annually and a minimum of 200 cases of percutaneous coronary angioplasty annually.
- (3) Medical institutions must have a minimum of one physician who has provided cardiovascular practice for at least 5 years and a minimum of one full-time physician who has provided cardiovascular surgery practice for at least 5 years.

IV Criteria for Indications of Elective PCI in Japan

1. Background

- It has been criticized that physicians in Japan have tried hard to improve their skills of PCI, but have failed to accumulate the data for evaluating the outcome of PCI, which resulted in insufficient analysis of indications.

- Because new devices and techniques of PCI have been launched in succession, indications for each device/technique have been discussed during the period of transition rather than the maturing period. Accordingly, the data of long-term studies published several years ago, which are the basis of discussion, are obsolete and do not reflect current treatment strategies.

2. Principles for Considering the Use of Elective PCI

Elective PCI for the treatment of stable CAD is indicated for patients with significant organic stenosis without unstable angina or acute myocardial infarction, who may or may not have anginal symptoms.

1. Lifestyle Intervention and Drug Treatment

Lifestyle intervention and drug treatment are essential components of the treatment of patients with stable CAD regardless of whether coronary revascularization is indicated or not. See Sections II and V.

2. Lifestyle Intervention, Drug Treatment, and Coronary Revascularization

Coronary revascularization relieves angina, improves exercise capacity, and reduces ischemia significantly. Although lifestyle measures and drug treatment for lifestyle-related diseases have evolved substantially, about one in every three patients with CAD does not respond well to these measures and requires coronary revascularization in addition to these measures.

- Combined therapy: (1) In initial medical therapy, patients receive lifestyle intervention and drug treatment, and those not responding well to these measures undergo coronary revascularization. (2) Patients may undergo coronary revascularization in an early phase of treatment in addition to drug treatment and lifestyle intervention (PCI plus medical therapy, if PCI is used).
- In low-risk patients with CAD, there is no difference in mortality between initial medical therapy and PCI plus medical therapy.^{5,9,42–46} However, inconsistent results have been reported in terms of the incidence of MACE such as ACS: Data of many studies conducted in Western countries showed no differences between initial medical therapy and PCI plus medical therapy, while the results of the JSAP and the SWISSI II (Swiss Interventional Study on Silent Ischemia Type II) study revealed better outcome of PCI plus medical therapy than initial medical therapy.^{5,9,42}

3. Criteria for Indications of PCI Based on the Data of Japanese Patients

Lifestyle intervention and drug treatment are first-line treatment for all patients with stable CAD. Especially patients suspected to have coronary spasm require treatment with long-acting calcium channel blockers, K_{ATP} channel openers, and long-acting nitrates as monotherapy or combined therapy. Anginal attacks should be treated with short-acting nitrates (sublingual).

1. Low-Risk Patients With CAD

In contrast to the COURAGE study⁵ and others conducted in Western countries, the results of the JSAP study,⁹ the first randomized clinical study comparing PCI plus medical therapy and initial medical therapy in Japan supported PCI plus medical therapy, which is commonly performed in Japan, for low-risk patients with CAD. In this guideline document, both PCI plus medical therapy and initial medical therapy are recommended. Initial medical therapy to follow the clinical course is an appropriate method for patients with mild anginal symptoms and/or ischemia, while for patients with obvious anginal symptoms or ischemia PCI plus medical therapy is an appropriate method as it may help to reduce drug dosages for symptomatic treatment. On the other hand, CAD patients with angina or ischemia not responding well to lifestyle intervention and drug treatment should not be managed only with drug treatment unless coronary revascularization is inappropriate. [Level of Evidence: C, consensus opinion of experts, small-scale clinical studies, results of sub-analysis, and others]

2. Patients With No Evidence of Ischemia

PCI is not indicated for patients in whom the absence of ischemia was documented.

3. Indications of PCI/CABG

See “Coronary Revascularization (PCI/CABG) for Stable Coronary Artery Disease: Statements and Indications Proposed by the Coronary Revascularization Council”.

V Management of Patients Undergoing PCI in Japan

1. Background

The most important strategy for patients after PCI is total patient care immediately before PCI, and discharge/outpatient management to ensure secondary prevention. See Chapter VI for restenosis, and Chapter VII for DES.

2. Acute-Phase Management After PCI

1. Bleeding Complications and Vascular Complications

- Brachial artery approach may cause hematoma. Surgical treatment is required when no radial artery pulse is felt and median nerve paralysis is present.
- When significant decreases in hematocrit and hemoglobin after PCI are present, the source of bleeding should be confirmed. Computed tomography (CT) is useful in the diagnosis of retroperitoneal hematoma. More than 80% of patients with retroperitoneal hematoma can be treated conservatively.⁴⁷

- When pseudoaneurysm develops and anticoagulation therapy may be discontinued, ultrasound-guided compression repair is beneficial.^{48–50}
- Arteriovenous fistula may be detected by palpable thrills or continuous murmur. Repeated punctures increase the risk of arteriovenous fistula. The incidence of vascular complications may be decreased with the use of recently introduced arterial puncture closing devices (to replace standard compression at the puncture site) and hemostatic devices.^{51,52}

2. Contrast-Induced Nephropathy

- Patients with underlying renal failure, those with diabetes and those prone to dehydration have a risk of renal dysfunction after the use of contrast media, and should be monitored for renal function after PCI.
- Contrast-induced nephropathy is defined as an increase in serum creatinine by $\geq 25\%$ or ≥ 0.5 mg/dL within 72 hours after PCI.
- Patients receiving contrast media with high osmotic pressure, those repeatedly receiving contrast media within 72 hours

after PCI, and those using intra-aortic balloon pump (IABP) should be carefully monitored for renal function.

- Predictive factors for the risk of contrast-induced nephropathy are a decrease in blood pressure, use of IABP, heart failure, chronic renal failure, diabetes, ≥ 75 years of age, anemia, and the dose of contrast media.
- Drugs with renal toxicity (e.g., antimicrobial agents, non-steroidal anti-inflammatory drugs and cyclosporine) and metformin should not be administered during the 48 hours before PCI.

3. Chest Pain and ECG Changes

- 12-lead electrocardiography (ECG) should be recorded before and after PCI.
- When chest pain develops after PCI, ECG monitors and 12-lead ECG should be inspected for ischemic ECG changes. When ischemic ECG changes are present, acute coronary occlusion or thromboembolism should be suspected,⁵³⁻⁵⁵ and repeat CAG and additional interventions should be considered.
- Risk factors for acute coronary occlusion are ≥ 70 years of age, extensive residual ischemia, ACS, and cardiac dysfunction (ejection fraction $< 30\%$).⁵³⁻⁵⁵

4. Increase in Creatine Kinase

- Increase in creatine kinase (CK) or CK-MB or abnormal ECG develop in 5 to 30% of patients undergoing PCI.⁵³
- An increase in CK is an independent predictive factor for cardiac death or myocardial infarction. The rate of cardiac death is significantly high among patients with a major increase in CK.^{56,57}

3. Chronic-Phase Management of Patients Undergoing PCI

1. Management of Coronary Risk Factors

The Guidelines for Secondary Prevention of Myocardial Infarction (JCS 2011)⁵⁸ prepared by the Japanese Circulation Society and the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases published in 2007⁵⁹ should be referred.

2. Exercise Stress Test

- Exercise stress test is useful in evaluating exercise capacity and severity of myocardial ischemia.
- Twenty-five percent of patients with ischemic change during exercise stress test are asymptomatic, and the presence of restenosis cannot be specified with chest pain or other symptoms. Especially, high-risk patients (low left ventricular ejection fraction [LVEF], multivessel CAD, proximal LAD stenosis, a history of sudden cardiac arrest, diabetes, left main CAD, and failed PCI) require appropriate examinations to detect myocardial ischemia.⁶⁰

- Stress ECG may detect 40 to 55% of restenosis cases.⁶¹⁻⁶³ Single photon emission computed tomography (SPECT) is effective in detecting ischemia.

3. Chronic-Phase CAG

- Routine follow-up CAG after PCI helps to detect restenosis and new lesions, although the optimal interval and duration of this follow-up are unknown. Routine follow-up CAG is commonly performed in Japan. [Class I, Level of Evidence: C]
- In patients receiving BMS with LMT disease, a high initial mortality after PCI (2% in the first month) has been suggested. Patients receiving BMS should undergo follow-up CAG 2 and 4 months after PCI⁶⁴ [Class IIa, Level of Evidence: C], and those receiving DES should undergo follow-up CAG 4 to 8 months after PCI.
- Multi-detector computed tomography (MDCT), a less invasive technique, is becoming available. CAG should be performed with careful consideration not to disadvantage patients.

4. Antiplatelet Therapy for Patients Undergoing PCI

Class I

- (1) Patients who have not received aspirin should receive aspirin (81 to 325 mg) before PCI (preferably, at least 2 hours before PCI). After PCI, patients should receive aspirin 81 to 162 mg/day over a lifetime, paying careful attention to the risk of bleeding. [Level of Evidence: A]
- (2) Patients who have not received clopidogrel should receive a loading dose of clopidogrel (300 to 600 mg) by at least 6 hours before PCI, and preferably should receive clopidogrel at 75 mg/day after PCI, paying careful attention to the risk of bleeding. [Level of Evidence: A]
- (3) After implantation of BMS or DES, it is preferable that patients receive combined therapy with aspirin (81 to 162 mg/day) and clopidogrel (75 mg/day). Recommended duration of therapy is at least one month for aspirin and at least 12 months for clopidogrel. [Level of Evidence: A]
- (4) Clopidogrel should be given to patients with contraindications to aspirin (e.g., patients with aspirin resistance or aspirin allergy). [Level of Evidence: B]
- (5) Patients with contraindications to clopidogrel should be treated with ticlopidine (200 mg/day). [Level of Evidence: A]

5. Anticoagulation Therapy for Patients Undergoing PCI

Heparin and argatroban.

Class I

Unfractionated heparin should be administered during PCI (activated coagulation time [ACT] 250 to 400 sec). [Level of Evidence: C]

Class IIa

Argatroban should be administered to patients with heparin-induced thrombocytopenia. [Level of Evidence: B]

VI Restenosis After PCI in Japan

1. Background

Because no well-conducted randomized clinical studies providing a high level of evidence on restenosis after PCI have been conducted in Japan, recommendations for measures to prevent restenosis after PCI were prepared on the basis of the

data of registry studies in Japan and mainly overseas data.

2. Percutaneous Old Balloon Angioplasty

- Restenosis rate after POBA is 32 to 40%.^{65,66}
- The causes of restenosis after POBA include neointimal pro-

liferation, and a reduction of vessel diameter referred to as negative remodeling or recoil.⁶⁷

Class IIa

Use of stents should be considered for restenosis lesions after POBA if the pathophysiology of restenosis is suitable for stenting. [Level of Evidence: B]

3. BMS

1. Facts and Factors of Restenosis After BMS

- Although restenosis rate is lower in BMS than in POBA, BMS may be associated with recurrent, highly intractable diffuse in-stent restenosis.
- BMS decreased the rate of major complications such as emergency bypass surgery due to dissection and/or acute coronary occlusion.
- The risk of in-stent restenosis is high for small vessel disease,⁶⁸ small postprocedural minimum luminal diameter,⁶⁹ high-grade residual stenosis,⁷⁰ LAD disease,⁶⁵ using long stents, diabetes,⁶⁸⁻⁷² and other factors.
- Causes of in-stent restenosis include neointimal proliferation within the stented segment, and neointimal proliferation and remodeling at the stent edge.

2. Restenosis After BMS in Japan

- Because BMS was approved in Japan in 1994 prior to approval in the United States, a high quantity of data such as long-term outcome and changes over time in luminal diameter have first been reported by researchers in Japan.⁷³
- The change in luminal diameter becomes constant and the neointima regresses at 6 months after BMS implantation. Follow-up for restenosis may be performed 6 months after BMS implantation.

4. Prevention of Restenosis by Using DES

See Chapter VII.

5. Other Measures to Prevent Restenosis

1. Drug Treatment to Prevent Restenosis

Class IIa

Use of cilostazol to prevent restenosis after PCI mainly using BMS. [Level of Evidence: A]

Class IIb or III

Use of drugs other than cilostazol to prevent restenosis after PCI. [Level of Evidence: B]

2. Prevention of Restenosis by Using Atherectomy

Class IIb or III

Use of PTCRA to prevent restenosis. [Level of Evidence: B]

PTCRA is necessary for patients with severe calcified lesions including patients receiving hemodialysis.⁷⁴

6. Intravascular Ultrasound Imaging

Class IIa

1. Assessment of the adequacy of stent expansion, including the extent of stent apposition and determination of the minimum in-stent luminal diameter. [Level of Evidence: B]
2. Determination of the mechanism of in-stent restenosis to enable a selection of appropriate therapy. [Level of Evidence: B]
3. Evaluation of coronary obstruction at a location difficult to image by angiography in a patient with a suspected flow-limiting stenosis. [Level of Evidence: C]
4. Evaluation of the results of PCI. [Level of Evidence: C]
5. Evaluation of the severity and distribution of calcified lesions during PTCRA. [Level of Evidence: C]
6. Determination of plaque location and circumferential distribution for guide of DCA. [Level of Evidence: B]

Class IIb

1. Determination of the extent of atherosclerosis in patients with characteristic anginal symptoms and a positive stress ECG result with no focal restenosis on angiography. [Level of Evidence: C]
2. Assessment of lesion characteristics and vessel diameter before PCI as a means to select an optimal revascularization device. [Level of Evidence: C]

Because the use of intravascular ultrasound imaging (IVUS) started to be covered by the NHI earlier in Japan than other countries, the technique is frequently used in Japan. In Western countries, this technique has been established as a commonly used imaging device to assess the characteristics of coronary lesions and the results of PCI, and the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention describe recommendations on IVUS.⁷⁵

7. Treatment Strategies for In-Stent Restenosis

Class I

Implantation of DES for the treatment of in-stent restenosis after BMS. [Level of Evidence: B]

Class IIa

Implantation of DES for the treatment of in-stent restenosis after DES. [Level of Evidence: C]

Class IIb

The use of cutting balloon angioplasty and other procedures in the treatment of in-stent restenosis after BMS. [Level of Evidence: A]

VII Use of DES in Japan

1. Background

- In Japan, the use of Cypher stents started to be covered by

the NHI in 2004.

- The manufacturing of Cypher stents was discontinued in 2011. As of January 2012, the use of TAXUS Liberté stents (Taxis Element stents), Endeavor stents, Xience V/Promus

stents, and Nobori stents are covered by the NHI in Japan.

2. Effectiveness of DES in the Prevention of Restenosis and Decreasing Repeat Revascularization

- DES significantly decreases the rates of restenosis (to $\leq 10\%$) and repeat revascularization through local administration of the drugs that inhibit the intimal proliferation. [Class I, Level of Evidence: A]

Class I

1. A DES should be considered as an alternative to the BMS in subsets of patients in whom trial data demonstrate efficacy and safety. [Level of Evidence: A]

Class IIb

1. At this point, the effectiveness and safety of DES have not been fully documented in published clinical trials, but the use of DES may be considered if the usefulness is expected from a clinical or an anatomical point of view. [Level of Evidence: C]
2. The use of DES may be considered for the treatment of short lesions in large (≥ 3.5 mm) vessels. [Level of Evidence: B].

3. Definition of Stent Thrombosis

Stent thrombosis is classified by elapsed time since stent implantation as follows:

- (1) Early stent thrombosis: 0 to 30 days after stent implantation
- (2) Late stent thrombosis: 1 to 12 months after stent implantation
- (3) Very late stent thrombosis: ≥ 1 year after stent implantation

4. Very Late Stent Thrombosis

- Very late stent thrombosis develops due to delayed neointimal coverage over stent struts.
- Very late stent thrombosis is not prevalent but is characteristics to DES. The incidence is about 2 to 3% in three years after stent implantation. The annual incidence ranges 0.4 to 0.6%.^{37,76}
- In the j-Cypher registry, the annual incidence of very late stent thrombosis during the five years after stent implantation was 0.26%, which is lower than those in Western countries.⁷⁷
- Data on incidence of very late stent thrombosis by stent type at this time are inconsistent.^{78–81}
- Predictive factors for stent thrombosis include bifurcation lesions, calcified lesions, clot volume, use of long stents, insufficient stent expansion, diabetes, ACS, left heart dysfunction, chronic renal failure, and early discontinuation of antiplatelet drugs.^{82–85} Different risk factors are involved in early, late and very late stent thrombosis.⁸⁶
- Stent thrombosis may trigger acute myocardial infarction. The mortality associated with stent thrombosis is high.

5. Long-Term Outcomes of DES Implantation

- The rates of restenosis and repeat revascularization after DES

implantation are lower than those after BMS implantation.

- Although DES implantation may be associated with very late stent thrombosis, overall rates of death and myocardial infarction are similar among DES- and BMS-treated patients.

6. Indications for DES

Class I

1. See the **Class I** recommendations in Section 2 “Effectiveness of DES in the Prevention of Restenosis and Decreasing Repeat Revascularization” of Chapter VII “Use of DES in Japan”.
2. Physicians should fully explain the importance of dual antiplatelet therapy, aspirin and a thienopyridine, and expected duration of treatment to patients before DES implantation to obtain patient’s understanding. [Level of Evidence: C]

Class IIb

See the **Class IIb** recommendations in Section 2 “Effectiveness of DES in the Prevention of Restenosis and Decreasing Repeat Revascularization” of Chapter VII “Use of DES in Japan”.

Class III

DES should not be used for patients who are expected to undergo invasive or surgical treatment that requires discontinuation of dual antiplatelet therapy within 6 months after stent implantation. [Level of Evidence: C]

7. Antiplatelet Therapy After DES Implantation

See Section 3. 4. “Antiplatelet Therapy for Patients Undergoing PCI” of Chapter V “Management of Patients Undergoing PCI in Japan”.

8. Measures for Patients Who Discontinued Antiplatelet Therapy After DES Implantation

- Antiplatelet therapy should not be discontinued in the early phase after DES implantation.⁸⁷
- Patients planning to undergo surgery should postpone surgery, or should be treated with BMS rather than DES.
- Patients should be instructed not to stop antiplatelet therapy without consulting with their physicians.
- During surgical or endoscopic procedures, discontinuation of both aspirin and thienopyridines should be avoided whenever possible.
- In patients who are planning to undergo surgery with a high risk of bleeding, the duration of discontinuation of both aspirin and thienopyridines should be shortest possible. In the j-Cypher registry, the incidence of stent thrombosis within 1 week after the discontinuation of antiplatelet therapy was low.
- Patients may receive intravenous heparin.

VIII Cost-Effectiveness Analysis of PCI in Japan

1. Background

- As the financial condition of the health insurance system deteriorates in Japan, cost-effectiveness assessment of health-care services becomes more important.
- Although cost-effectiveness analyses are essential to ensure effectiveness and efficacy of PCI, few reports have been published in Japan.

2. Initial Medical Therapy vs. PCI Plus Medical Therapy

- Although the healthcare cost of PCI plus medical therapy is higher than that of initial medical therapy,^{88,89} PCI plus medical therapy is effective in alleviating symptoms promptly. In the JSAP study, the incidence of cardiovascular accidents was lower in patients receiving PCI plus medical therapy than those receiving initial medical therapy.⁹ Although further analyses should be performed to evaluate total healthcare cost including short- and long-term outcome and efficiency of treatment, a strategy optimal for each patient should

be selected according to his/her preference and lifestyle.

3. Comparison Between PCI and CABG in the BMS Era

Although the initial cost is higher for CABG than for PCI, the difference has been decreasing over time. The cost-effectiveness of PCI may decrease over time as compared with CABG.

4. Comparison Between BMS and DES

The accumulated three-year cost for DES is lower than BMS by about 200,000 yen. In Japan's NHI system, the use of DES is expected to decrease healthcare cost as compared with BMS.⁹⁰

5. Comparison Between DES and CABG

No data are available.

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Appendix 1. JCS Joint Working Group

Chair:

- Hisayoshi Fujiwara, Hyogo Prefectural Amagasaki Hospital/Hyogo Prefectural Tsukaguchi Hospital

Members:

- Hiroyuki Daida, Department of Cardiovascular Medicine, Juntendo University School of Medicine
- Atsushi Hirayama, Division of Cardiovascular Medicine, Department of Medicine, Nihon University School of Medicine
- Takaaki Isshiki, Department of Medicine, Teikyo University School of Medicine
- Takeshi Kimura, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine
- Izuru Masuda, EBM Center for Preventive Medicine, Takeda Hospital Group
- Kazuaki Mitsudo, Heart Disease Center, Kurashiki Central Hospital
- Shunichi Miyazaki, Division of Cardiology, Department of Internal Medicine, Kinki University School of Medicine
- Hiroshi Nishida, Department of Cardiovascular Surgery, The Heart Institute of Japan, Tokyo Women's Medical University
- Kazuhiko Nishigaki, Department of Cardiology, Gifu University Graduate School of Medicine
- Masami Ochi, Department of Cardiovascular Surgery, Nippon Medical School Graduate School of Medicine
- Satoshi Ogawa, International University of Health and Welfare, Mita Hospital
- Takayuki Ohno, Department of Cardiovascular Surgery, Mitsui Memorial Hospital
- Ryuzo Sakata, Department of Cardiovascular Surgery, Kyoto University Graduate School of Medicine
- Teruo Shiba, Division of Diabetes and Metabolism, Toho University Medical Center, Ohashi Hospital
- Tetsuya Sumiyoshi, Department of Cardiology, Sakakibara Heart Institute
- Takahiko Suzuki, Toyohashi Heart Center
- Shinichi Takamoto, Mitsui Memorial Hospital
- Hitoshi Yaku, Division of Cardiovascular Surgery, Department of Surgery, Kyoto Prefectural University of Medicine
- Tsutomu Yamazaki, Clinical Research Support Center, The University of Tokyo Hospital

Independent Assessment Committee:

- Tadanori Aizawa, The Cardiovascular Institute
- Tohru Asai, Division of Cardiovascular Surgery, Department of Surgery, Shiga University of Medical Science
- Masatoshi Fujita, Uji Hospital
- Kyoichi Mizuno, Division of Cardiology, Hepatology, Geriatrics and Integrated Medicine, Department of Internal Medicine, Nippon Medical School

- Masanori Nomura, Division of Cardiology, Banbuntane Hotokukai Hospital, Fujita Health University
 - Hisao Ogawa, Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University/National Cerebral and Cardiovascular Center
 - Tadashi Tashiro, Department of Cardiovascular Surgery, Fukuoka University School of Medicine
 - Chuwa Tei, Dokkyo Medical University
- (The affiliations of the members are as of September 2012)

Appendix 2. Coronary Revascularization Council

Chair:

- Satoshi Ogawa, International University of Health and Welfare, Mita Hospital

Members:

- Hiroyuki Daida, Department of Cardiovascular Medicine, Juntendo University School of Medicine
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