Ischemia-Guided Percutaneous Coronary Intervention for Patients With Stable Coronary Artery Disease
Young-Hak Kim, MD, PhD; Seung-Jung Park, MD, PhD

Current evidence and guidelines support the strategy of ischemia-guided revascularization for treatment of patients with stable coronary symptoms. However, anatomical stenosis is often targeted in revascularization treatment using percutaneous coronary intervention or coronary artery bypass surgery without seriously considering objective evidence of myocardial ischemia. Particularly, for patients with multivessel disease, angiographic complete revascularization was traditionally considered an ideal objective of revascularization treatment. Recently, however, observational studies contradict the concept of angiographic complete revascularization and support the benefit of ischemia-guided selective revascularization based on noninvasive and invasive functional evaluation detecting ischemia-producing coronary lesions. In the absence of a trial specifically designed to assess the relative benefit of either strategy, the present review explores the current concepts about the strength and weakness of anatomical vs. functional revascularization. (Circ J 2013; 77: 1967–1974)

Key Words: Coronary artery disease; Ischemia; Stents

For stable coronary artery disease (CAD), the role of coronary revascularization using percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery remains controversial. Although the guidelines do not support prompt revascularization for patients with stable coronary symptoms, this is not properly integrated into clinical practice. For example, coronary angiography or computed tomography (CT) is considered the standard for anatomical evaluation, despite substantial discrepancies between angiographic findings and the functional severity of stenosis. Recent advances in drug-eluting stents (DES) and adjuvant pharmacologic agents have reduced the threshold for PCI in the absence of myocardial ischemia. This review evaluates (1) the clinical implications of angiography-guided revascularization, (2) the methods used to detect myocardial ischemia, and (3) the benefits of ischemia-guided revascularization in PCI for patients with stable CAD.

Angiographic Complete Revascularization (CR)

Definition
The definition of angiographic CR has varied depending on the patient population and whether PCI or CABG is the treatment. Although the traditional definition of CR was total revascularization of lesions >1.5 mm in diameter and with >50% stenosis, several studies have defined CR relative to vessels with >70% stenosis. In addition, practical definitions have been applied to proximal segments or vessels >2.5 mm in diameter because the available stents were >2.5 mm.

The prevalence of CR is found to differ between PCI and CABG procedures. When the traditional definition of CR is applied to all coronary segments, the success rate among patients is <50%. However, using the definition for larger vessels (>2.5 mm) or tighter stenosis (>70%), the success rate was >60%. Because CR is attempted during most CABG operations, it has most often been achieved after CABG, with a success rate >70%. It is noteworthy that incomplete revascularization (IR) was not uncommon following either PCI or CABG.

Outcomes
CR was traditionally considered the strongest predictor of improved clinical outcome (Table). This observation was based on long-term studies on outcomes, focusing on the relationship between the extent of revascularization and the reduction of adverse events. In a clinical setting, the strategy of CR or IR was often determined by the presence of significant comorbidities and anatomical angiographic complexity. In fact, IR was often a marker for serious comorbidity and complex coronary anatomy, such as depressed ventricular function, chronic lung disease, renal failure, multivessel disease, left main stenosis, and calcified lesions. Differences in baseline characteristics between patients treated with either CR or IR were confounders, which influenced the true effect of CR. As a result, the clinical effect of CR has been debated in the literature and has not been consistent across studies.
Table. Studies Comparing Angiographic Complete Versus Incomplete Revascularization for Patients With Non-Acute Coronary Symptoms

<table>
<thead>
<tr>
<th>Date</th>
<th>Duration</th>
<th>Design</th>
<th>Type of stent</th>
<th>Definition of completeness</th>
<th>Significant lesion</th>
<th>No. of patients</th>
<th>Age, years</th>
<th>LVEF, %</th>
<th>Diabetes, %</th>
<th>SYNTAX score</th>
<th>LVEF &lt;35, %</th>
<th>3-vessel disease, %</th>
<th>Total occlusion, %</th>
<th>MACCE, %</th>
<th>All-cause death, %</th>
<th>Cardiac death, %</th>
<th>MI, %</th>
<th>Stroke, %</th>
<th>Repeat revascularization, %</th>
<th>MACE, %</th>
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<td>DES</td>
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<td>31</td>
<td>DES</td>
<td>IR</td>
<td>CR</td>
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*Propensity-matched subset of each registry. †Presented as a percentage of diameter stenosis in a vessel of a certain diameter. Terms in parentheses mean definitions of coronary artery segments used in each study. §Segment means revascularization of all diseased segments; major CA, revascularization of all diseased major coronary artery. ⑪P<0.05 between IR vs. CR.

In the era of the bare-metal stent (BMS), the ARTS (Arterial Revascularization Therapies Study) group investigated the prevalence of CR, defined as revascularization of lesions >1.5 mm in diameter and with >50% stenosis, in 1,205 patients randomly treated by either PCI with BMS or CABG. They reported that the prevalence of CR was 71% after PCI and 98% after CABG. After 1 year, the incidence of major adverse cardiac and cerebrovascular events (MACCE), including death, myocardial infarction (MI), stroke or repeat revascularization, was lower after PCI in the CR group than in the IR group (23.4% vs. 30.6%, respectively, P<0.05). After CABG, the incidence of MACCE was similar in these 2 groups (10.1% vs. 12.2%, respectively). This finding was supported by results from the New York State PCI Registry, which enrolled 21,945 patients receiving BMS. CR for lesions with >50% stenosis was performed in 69% of patients, with different hospitals reporting rates ranging from 52% to 88%. Over 3 years, the adjusted survival rate was 91.4% in the CR group, and 89.5%, 88.8%, and 88.7% in patients with ≥2-vessel IR, total occlusion, and ≥1-vessel IR plus total occlusion, respectively. Therefore, the adjusted hazard ratio (HR) of IR for survival was 1.15 (95% confidence interval [CI], 1.01–1.30) compared with CR. After PCI with DES, CR was still an important predictor of a favorable long-term prognosis. For example, out of 11,394 patients in the New York State Registry who underwent DES implantation, 39% underwent CR. The risk-adjusted survival rates were 93.8% in the IR group and 94.9% in the CR group (HR, 1.23, 95% CI, 1.04–1.45). In the 3,803 propensity-score matched pairs, the 8-year survival rate was higher after CR than IR (80.8% vs. 78.5%; HR, 1.12; 95% CI, 1.01–1.26; P=0.04). Based on those findings, it was recommended that patients with multivessel disease undergo CABG if CR was not expected to be successful by PCI. Regarding the effect of CR on CABG, a Swedish hospital registry reported that IR in >1 diseased vessel was associated with an increased risk of 5-year mortality (HR, 1.82; 95% CI, 1.15–2.85). However, the vast majority of registries showed that anatomical CR was not associated with long-term adverse outcomes in patients undergoing CABG. In a study of the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial, which compared the outcomes of PCI with DES vs. CABG for patients with multivessel or left main disease, patients with CR by PCI had lower rates of MACCE (66.5% vs. 76.2%, P<0.001), composite safety endpoints (83.4% vs. 87.9%, P=0.05) and...
repeat revascularization (75.5% vs. 83.9%, P<0.001), but not of death or MI. However, in the CABG group, no difference in outcomes was seen between the IR and CR groups.

For 2,686 patients presenting with non-ST elevation acute coronary syndromes in a substudy of the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial, the residual SYNTAX score was a strong and independent predictor of 1-year death or MI, having a good discriminatory power for values >8. The residual SYNTAX score was the univariable score observed after PCI. Following PCI, only 40.4% of patients achieved CR with a residual SYNTAX score=0. There was a gradual increase in the incidence of death, MI, and unplanned revascularization when patients were grouped according to residual scores of 0, >0–2, ≥2–8, and >8. In addition, the residual score was an independent predictor of death (HR, 1.05; 95% CI, 1.03–1.08; P<0.001), MI (HR, 1.02; 95% CI, 1.01–1.04; P=0.003), and unplanned revascularization (HR, 1.04, 95% CI, 1.02–1.05; P<0.001). In the multivariate analysis, IR for lesions with ≥50% stenosis in vessels ≥2.0 mm was an independent predictor of 1-year major adverse cardiac events including death, MI, and ischemia-driven unplanned revascularization (HR, 1.36; 95% CI, 1.12–1.64; P=0.002).

Despite the aforementioned studies showing superior results with CR, a recent study from the Asan Multivessel Registry failed to show a connection between CR and long-term clinical outcomes. Of 1,914 patients with multivessel disease undergoing DES implantation (1,400 patients) or CABG surgery (514 patients), 917 patients (47.9%) underwent angiographic CR for lesions with >50% stenosis and >1.5 mm in diameter, including 573 (40.9%) patients undergoing PCI and 344 (66.9%) patients undergoing CABG. After 5 years, the incidence of MACCE was similar in patients with CR and IR (22.4% vs. 24.9%, respectively; adjusted HR, 0.91; 95% CI, 0.75–1.10; P=0.32). Even when CR was defined as lesions >2.5 mm in diameter or proximal lesions, it remained a nonsignificant predictor of 5-year MACCE. However, 368 (19.2%) patients with multiple unirevascularized vessels had a higher rate of MACCE (30.3% vs. 22.1%; adjusted HR, 1.27; 95% CI, 0.97–1.66; P=0.079).

The discrepancy between the results of the Asan registry and those of other studies may be because of differences in patient characteristics and procedural techniques. Nonetheless, the studies consistently indicated that ‘reasonable IR’ is a more reliable approach for patients with multivessel disease. Because of the limitations of anatomic evaluation and the potential advantages of functional evaluation, physicians should emphasize the importance of adhering to guidelines. It is not reasonable to revascularize all coronary lesions without a functional assessment.

**Evaluation of Myocardial Ischemia**

**Mismatch Between Anatomical and Functional Stenosis**

Inducible myocardial ischemia during functional testing has crucial prognostic significance in determining whether or not to treat coronary artery stenosis. Of note is that angiographic stenosis is not equivalent to functionally significant stenosis. In a study using SPECT myocardial perfusion imaging, 77 (54%) patients had either no perfusion defects or only 1-vessel disease pattern among 143 patients with angiographic 3-vessel disease. Another single-photon emission tomography (SPECT) study showed that 50 of 67 patients with angiographic multivessel disease had no defects or only 1 segmental perfusion defect. Similar findings were observed in the FAME (Flow Reserve vs. Angiography for Multivessel Evaluation) study. Of all the patients visually diagnosed with 3-vessel disease, only 14% actually had it and 9% had no functionally significant stenosis based on fractional flow reserve (FFR) measurement. Furthermore, of the lesions with stenosis between 50% and 70%, 71% and 90%, and 91% and 99%, only 65%, 20%, and 4%, respectively, were found to have FFR >0.80. These findings highlight the pivotal role of a functional evaluation using both noninvasive and invasive methods in detecting functionally stenotic CAD requiring revascularization.

**Noninvasive Evaluation**

Functional evaluation prior to revascularization has been underutilized in clinical practice. In a recent analysis, only 44.5% of 23,887 patients with stable angina underwent treadmill exercise or pharmacological stress testing and myocardial imaging within 90 days of elective PCI. Interestingly, high PCI volume (≥150 cases per year) and physician age (50–69 years old compared with <40 years old) were found to be significant predictors of the likelihood to patients undergoing stress testing prior to elective PCI. Estimates of the sensitivity and specificity of noninvasive tests vary substantially. For patients who are able to exercise, exercise ECG is the primary recommendation to detect ischemic CAD. However, it is limited in its ability to detect ischemic territory, so it is not a useful way to guide PCI for lesions provoking ischemia.

Among the noninvasive tests, SPECT has been most widely validated in clinical practice. Across studies, a significant relative risk associated with abnormal studies and a very high negative predictive value for normal studies has been demonstrated in more than 19,000 patients. Follow-up studies were performed for as long as 6 years. The association between quantitatively measured stress-induced ischemia and prognosis was recently evaluated in a nuclear substudy of clinical outcomes. That study evaluated the outcome of 314 patients receiving SPECT before treatment, of a total of 2,287 randomized patients with either optimal medical therapy alone or revascularization plus medical therapy in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial. A significant reduction in myocardial ischemia (≥5%) was achieved in 33% of patients in the revascularization group and in 19% of patients in the medical therapy alone group (P=0.004). Patients with a reduction in ischemia were less likely to die or experience MI (P=0.037).

Although SPECT is the most widely used and validated perfusion imaging technique, it is limited by relatively low resolution. Particularly for patients with multivessel disease or left main stenosis, balanced ischemia in the myocardium sometimes leads to false-negative results following SPECT. When the diagnostic accuracy for multivessel disease and left main stenosis was compared between SPECT and stress echocardiography in a meta-analysis, stress echocardiography showed a better discriminatory capacity than SPECT. The usefulness of stress echocardiography was evidenced by numerous studies enrolling over 5,000 patients for observation periods of more than 3 years. Similarly to SPECT, stress echocardiography is also associated with a high rate of subsequent cardiac events, and a normal stress echocardiogram is associated with a low incidence of adverse events. However, clinical research on the clinical applicability of stress echocardiography is still limited when compared with SPECT.

More recently, cardiac magnetic resonance (MR) imaging and positron emission tomography (PET) have been used. A recent meta-regression analysis showed that both cardiac MR and PET have significantly higher diagnostic accuracy than...
SPECT on both a patient and coronary territory basis. The advantage of PET over SPECT could be explained by its higher spatial resolution, excellent attenuation correction, and the use of different tracers. Cardiac MR perfusion imaging has the advantage of fewer attenuation artifacts and high spatial resolution. In spite of their high sensitivity and specificity, widespread use of PET or MR is currently hampered by high costs and limited availability.

In clinical experiments, the role of stress perfusion CT or noninvasive FFR computed CT (FFR_{CT}) is also being evaluated. CT stress myocardial perfusion imaging and FFR_{CT} are promising methods to detect myocardial ischemia. CT perfusion images are acquired as contrast transits the coronary arteries into the myocardium. This can be performed during rest or stress induced by a vasodilator, such as adenosine, regadenoson, or dipyridamole. In the absence of artifacts, hypotenuated areas in the myocardium on CT represent areas of reduced perfusion. Although there is debate on the imaging protocol, early studies of CT stress myocardial perfusion imaging showed good diagnostic accuracy compared with SPECT, MR, or invasive FFR. Figure 1 shows an example of a patient with CAD having normal thallium SPECT and abnormal CT perfusion imaging. FFR_{CT} is another application of CT to detect myocardial ischemia using a noninvasive calculation of FFR from CT-derived from the computational fluid dynamics.

**Invasive Evaluation**

FFR is a pressure-derived index that was developed in the early 1990s and is calculated using an invasive pressure wire. FFR is defined as the ratio of maximal hyperemic myocardial blood flow through a stenotic artery to the theoretical maximal hyperemic myocardial blood flow in the absence of stenosis. FFR is calculated by measuring distal mean coronary and aortic pressures during maximal hyperemia using a 0.014-inch pressure sensor angioplasty guidewire. FFR describes the influence of coronary stenosis on maximal perfusion of the sub-

**Figure 1.** Coronary evaluation of anatomical and functional abnormalities. A patient with significant left anterior descending artery stenosis identified by coronary angiography (A) and CT angiography (B) had a normal thallium SPECT (C), but perfusion defects in the matched territory of CT myocardial perfusion after adenosine-induced stress image (D-1) compared with the rest image (D-2).
Several studies have been performed to assess the natural course of anatomical lesions without functional ischemia. Nuclear imaging studies have suggested that treatment of nonischemic coronary lesions may be safely deferred. In a meta-analysis of thallium SPECT, the annual incidence of death or MI was only 0.6%. The DEFER (FFR to Determine Appropriateness of Angioplasty in Moderate Coronary Stenoses) study

**Ischemia-Guided PCI**

**Natural Course of Lesions Without Inducible Ischemia**

Several studies have been performed to assess the natural course of anatomical lesions without functional ischemia. Nuclear imaging studies have suggested that treatment of nonischemic coronary lesions may be safely deferred. In a meta-analysis of thallium SPECT, the annual incidence of death or MI was only 0.6%. The DEFER (FFR to Determine Appropriateness of Angioplasty in Moderate Coronary Stenoses) study
evaluated the 5-year outcomes in 325 patients assigned to 1 of 3 groups: deferred group (FFR ≥0.75 without PCI [n=91]), PCI group (FFR ≥0.75 with PCI [n=90]), and a control group (FFR <0.75 with PCI [n=144]). Interestingly, 5-year event-free survival rates were similar in the deferred and PCI groups (80% vs. 73%, respectively; P=0.52). The composite rates of cardiac death and acute MI in the deferred, PCI, and control groups were 3.3%, 7.9%, and 15.7%, respectively. Therefore, the 5-year risk of cardiac death or MI in patients with normal FFR is <1% per year. A recent 2-year outcome of the FAME study supported the safety of deferring PCI for nonischemic lesions. Among 513 patients with lesions deferred based on FFR value, only 1 patient (0.2%) experienced MI and only 16 patients (3.2%) required repeat revascularization.

Clinical Outcomes
Unnecessary revascularization of nonischemic coronary vessels may lead to increased medical costs and deterioration in clinical prognosis. The ACIP (Asymptomatic Cardiac Ischemia Pilot) study in the 1990’s was carried out to assess the benefits of ischemia-guided revascularization. In that study, 558 patients with ischemia were randomly allocated to 1 of 3 groups: PCI guided by angina (n=183), angina plus ischemia (n=183), and angiography (n=192). After 2 years, mortality was 6.6% in the angina-guided group, 4.4% in the ischemia-guided group, and 1.1% in the prompt revascularization group (P<0.02). The incidence of death or MI was 12.1% in the angina-guided group, 8.8% in the ischemia-guided group, and 4.7% in the prompt revascularization group (P<0.04).

More recently, in the FAME study, 1,005 patients with multivessel CAD were randomly assigned to undergo PCI with or without FFR measurement. The number of stents placed was 1.9±1.3 in the FFR group and 2.7±1.2 in the non-FFR group (P<0.001). After 1 year, the relative risk of death or MI was 0.66 (95% CI, 0.44–0.98) in the FFR group compared with the non-FFR group. The 2-year incidence of death or MI was significantly lower in the FFR-guided patients than in the angiography-guided patients (8.4% vs. 12.9%, respectively; P=0.02), although the increased event rate in the latter group may have been related to the use of more complex procedures using more stents. Consequently, a cost-utility analysis showed that FFR-guided stenting significantly decreased 1-year medical costs with the same risk of events. FFR-guided stenting significantly decreased 1-year medical costs with the same risk of events. Consequently, a cost-utility analysis showed that FFR-guided stenting significantly decreased 1-year medical costs with the same risk of events. FFR-guided stenting significantly decreased 1-year medical costs with the same risk of events.

The ischemia-guided procedure involves evaluation of functional rather than anatomical revascularization strategy. The FAME-2 trial tested the benefits of FFR-guided PCI with optimal medical therapy for stable CAD. It showed that 4.3% of patients in the PCI group compared with 12.7% in the medical therapy group (HR, 0.32; 95% CI, 0.19–0.53; P<0.001) had a primary endpoint event of death, MI, or urgent revascularization. Because of this significant between-group difference, recruitment was halted prematurely after enrolment of 1,220 patients. The difference was driven by a lower rate of urgent revascularization in the PCI group than in the medical therapy group (1.6% vs. 11.1%; HR, 0.13; 95% CI, 0.06–0.30; P<0.001).

Studies in nonrandomized observational cohorts have been carried out to assess the benefits of ischemia-guided revascularization. Hachamovitch et al highlighted the relationship between the amount of inducible ischemia present on SPECT and the presence of short-term survival benefits with early revascularization vs. medical therapy. Of 10,627 patients who underwent SPECT imaging without a prior history of MI or revascularization, revascularization was associated with a reduction in mortality for patients having moderate to severe ischemia. The cut-off level of ischemic myocardium to predict lower mortality using revascularization was approximately 10–12.5%, as assessed by summed stress scores. Kim et al. supported the benefit of ischemia-guided revascularization with a large single center PCI cohort. Of 2,587 patients who underwent PCI using DES, ischemia-guided PCI, defined as PCI for ischemic arteries identified with SPECT imaging, was performed in only 12.4% of patients. Ischemia-guidance reduced the incidence of MACCE compared with nonischemia-guidance (17.4% vs. 22.8%; adjusted HR, 0.59; 95% CI, 0.43–0.81; P=0.001), driven by a lower incidence of repeat revascularization (9.9% vs. 14.8%; adjusted HR, 0.53; 95% CI, 0.35–0.80; P=0.003). A multicenter study performed in Japan showed that patients receiving initial SPECT had a lower rate of revascularization than those receiving coronary angiography (odds ratio, 5.36; 95% CI, 4.07–7.05). Another large registry study in Japan showed the risk of cardiac death, MI, and congestive heart failure requiring hospitalization was reduced by coronary revascularization for patients with moderate to severe ischemia, but not for those with mild ischemia on SPECT imaging. These studies indicate that ischemia-guided PCI may reduce the cost, radiation exposure and procedural complications by avoiding unnecessary, complex procedures and consequently improving long-term prognosis.

The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial will target patients with more severe ischemia than those in the COURAGE trial. It was designed to compare the effectiveness of initial medical treatment vs. revascularization for patients with moderate or severe ischemia on myocardial perfusion imaging. This trial may better clarify the benefits of ischemia-guided revascularization for stable CAD patients.

Conclusion
Current evidence and guidelines support the strategy of ischemia-guided revascularization for treatment of stable angina. The ischemia-guided procedure involves evaluation of functional myocardial ischemia using noninvasive or invasive tests, such as SPECT, PET, MR perfusion, or FFR. A CT-guided approach is also being investigated through the new concept of stress coronary perfusion or virtual FFR. After assessing ischemia-producing coronary lesions, PCI or CABG will be a functional rather than anatomical revascularization strategy. Additional research to compare the strategies of function-guided vs. anatomy-guided revascularization in a randomized study design will provide strong evidence favoring ischemia-guided revascularization in the future.

References


