What Can We Expect in PCI in Patients With Chronic Coronary Artery Disease

– Indication of PCI for Angiographically Significant Coronary Artery Stenosis Without Objective Evidence of Myocardial Ischemia (Con) –

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Compared with coronary artery bypass graft surgery (CABG), similar safety and efficacy have been demonstrated for percutaneous coronary intervention (PCI) with bare metal stents (BMS), except for the inferiority of PCI to CABG for repeat revascularization. Drug-eluting stents (DES) have dramatically reduced in-stent restenosis compared with BMS, and comparable prognoses could be expected in PCI with DES compared with CABG. Nevertheless, the long-term prognostic effect of PCI on major adverse cardiovascular events (MACE) in patients with stable coronary artery disease (CAD) remains uncertain, so the spotlight has been focused on the comparative long-term results of DES and CABG. At the moment, we should know that previous studies have reported only that PCI decreases angina frequency and improves short-term exercise performance in chronic CAD patients, and it effectively reduces the incidence of both death and myocardial infarction (MI) only in patients with acute coronary syndromes. Furthermore, a recent study also describes no advantage in improvement of prognosis including death, MI and other MACE for PCI compared with aggressive medical therapy in stable CAD patients, and for stenotic lesions without evidence of ischemia, the benefit of revascularization is less clear; medical therapy alone is likely to be equally effective. In conclusion, based on these data we should restrain ourselves from lesion treatment by simple PCI for angiographically significant CAD without any objective evidence of myocardial ischemia. (Circ J 2011; 75: 211–217)

Key Words: Coronary artery bypass grafting; Coronary artery disease; Ischemia; Percutaneous coronary intervention (PCI); Stents

Several randomized controlled trials that compared percutaneous coronary intervention (PCI) with bare metal stents (BMS) and coronary artery bypass graft surgery (CABG) have demonstrated a similar safety profile and efficacy for PCI, excepting the significantly higher risk of PCI for repeat revascularizations resulting from in-stent restenosis and new lesions proximal or distal to the culprit site.1–8 Recently developed drug-eluting stents (DES) have dramatically reduced in-stent restenosis compared with BMS,5–17 and comparable prognoses could be expected in PCI with DES as compared with CABG. Thus, comparative long-term follow-up results between PCI with DES and CABG, or the advantages of PCI with DES compared with CABG are in spotlight recently, with a lack of fundamental discussion whether PCI may really improve prognosis in patients with coronary artery disease (CAD).18–25 However, previous reports have described PCI reducing the incidence of death and myocardial infarction (MI) in patients who present with acute coronary syndromes (ACS),26–31 although a similar benefit has not been shown for patients with stable CAD.32–36 Furthermore, although successful PCI of flow-limiting stenoses might be expected to reduce the rate of death, MI, and hospitalization for ACS, previous studies have shown only that PCI decreases the frequency of angina and improves short-term exercise performance.32,33,36 Thus, the long-term prognostic effect of PCI on cardiovascular events in patients with stable CAD remains uncertain.37 Moreover, the recent COURAGE trial has demonstrated no advantage in prognosis including death, MI and other major adverse cardiovascular events (MACE) for PCI with BMS compared with aggressive medical therapy in patients with stable CAD,37 and the spotlight has been focused again on improvement of prognosis in CAD regardless of the type of treatment. The COURAGE nuclear study has revealed, furthermore, the importance of the degree of both the baseline ischemia and the reduction of ischemia in PCI.38 Moreover, the recent FAME study emphasized the advantage of ischemia-oriented PCI to anatomy-oriented PCI by coronary angiography (CAG) in reducing the rate of the
primary composite endpoint of death, MI, and repeat revascularization at 1 year and the combined rate of death and MI in patients with multivessel CAD. These reports direct us to discuss whether PCI with BMS or DES would really improve the prognosis of CAD patients and whether PCI could improve symptoms alone without any improvement of the prognosis in stable CAD. 

Prognosis of CAD

Since the development of medical therapy, including various primary and secondary preventative regimens, it might be difficult to know the real natural history of a patient with CAD without any medication. In this setting, the CASS registry and the ACCF/SCAI/STS guidelines have demonstrated poor prognosis in medically treated patients with CAD in proportion to the increase in the number of diseased vessels, and in the registry the 12-year survival was only 40% in patients with 3-vessel disease and 59% and 74% in those with 2- and 1-vessel disease, respectively (P<0.0001). Even in patients with 0-vessel disease in this registry, the 12-year survival of patients with normal coronary arteries was 91%, compared with 86% for those with minimal lesions and 79% for those with moderate lesions. In addition to the number of diseased vessels, the presence of >50% left main coronary artery (LMCA) stenosis had an additional impact on survival in patients with at least 2-vessel disease, and the 12-year survival of patients with 2-vessel disease involving the LMCA was 49%, compared with 60% for those without LMCA disease. For patients with 3-vessel disease involving the LMCA, survival was 35%, compared with 41% for those with 3-vessel disease without LMCA involvement (P<0.0001). Furthermore, left ventricular ejection fraction (LVEF) also had another great impact on survival in CAD patients, as has been pointed out previously. Patients in the CASS registry who had at least 1 diseased vessel and LVEF in the range of >50%, 35–49%, or <35% had 12-year survival of 73%, 54%, and 21%, respectively (P<0.0001). Within the 1-, 2-, and 3-vessel disease subgroups, LVEF remains a very important predictor of survival. The 12-year survival of patients with 3-vessel disease and LVEF in the range of >50%, 35–49%, or <35% was 58%, 35%, and 10%, respectively (P<0.0001). Furthermore, for each LVEF category, survival decreased according to the number of vessels obstructed. Patients with 1-vessel disease or 2-vessel disease and normal LV function who have been managed medically have maintained a good survival history and no prognostic improvement by PCI or CABG could be demonstrated. Although there is a Japanese trial that demonstrated a reduction in ACS incidence by PCI with medical therapy compared with initial medical therapy in low-risk patients, no survival improvement was demonstrated in that study. Thus, as described previously, only in cases of 3-vessel disease and poor LV function, can improvement of survival be expected even by CABG. Furthermore, because much greater long-term patency can be expected with a left internal mammary artery graft to the left anterior descending artery, a much better prognosis can be assumed for CABG. To date, there have been no data in the literature demonstrating the advantages of PCI, even with DES, over CABG.

Identification of Significant Coronary Artery Stenosis

It is well known that significant CAD is diagnosed clinically by the agreement of the presence of myocardial ischemia and the demonstration of a culprit lesion that can explain the inducible ischemia. The culprit site of ischemia is assessed by anatomical evaluation such as CAG, multislice CT (CTCA), whole heart magnetic resonance imaging (MRI), intravascular ultrasound (IVUS), optical coherence tomography, and so on. The suggestion of ischemia is proved by physiological assessment such as thallium scintigraphy, stress echocardiography, MRI perfusion image, pressure-derived fractional flow reserve (FFR), and so on. Originally, CAG was the gold standard for assessing the severity of a coronary artery, and in routine clinical practice it is still the gold standard for the assessment of coronary stenosis. However, the limitations of CAG have also been clearly described by IVUS studies and autopsy studies. Because CAG is simply luminography based on visualizing a vessel lumen filled by contrast agent, and the stenosis severity is simply evaluated by visual estimation of the degree of stenosis as the ratio of the most stenotic portion to the reference vessel. Thus, even in multiple projections, intermediate lesions and complex lesions, such as diffuse lesions, bifurcation lesions, and ostial lesions, might be difficult in theory to estimate, especially if there are several atherosclerotic lesions even in the reference vessel and even if we evaluate CAG quantitatively. CTCA is now challenging conventional diagnostic CAG with a sensitivity and specificity of 92% in a recent pooled analysis of studies using 64-slice CT. As reported previously, however, CTCA will not be the gold standard for estimating significant coronary lesions because of its high negative predictive values and low positive predictive values in comparison with CAG. Neither conventional CAG nor CTCA can accurately predict the functional significance of coronary stenosis. Thus, anatomical estimation has limitations for diagnosing significant coronary stenosis or stenoses, even if CAG has been thought to be the gold standard. Therefore, in patients with stable CAD and multivessel disease in particular, identification of the culprit stenosis or stenoses would be required anatomical assessment by CAG in daily clinical practice, and the number of diseased vessel would have a risk to be misread in daily clinical practice in catheterization laboratory.

Physiological assessment of coronary lesion severity has been developed as an objective demonstration of the presence of inducible ischemia, and in most cases has been validated by comparison with quantitative CAG (QCA) or visual assessment of the degree of stenosis as the gold standard test. In a pooled analysis of 79 studies, SPECT demonstrated a mean sensitivity of 86% and specificity of 74%, varying according to which radioisotope was used. The combination of dobutamine stress and myocardial contrast echocardiography provides a sensitivity of 91% and specificity of 70%, which is comparable to SPECT, although several studies described significantly superior sensitivity and specificity for stress echocardiography compared with thallium scintigraphy. The sensitivity and specificity of the MRI myocardial perfusion image for the detection of significant CAD were
recently evaluated in a meta-analysis of 24 studies and found to be 91% and 81%, respectively.\(^23\) However, as stated previously, the majority of these studies used QCA or visual assessment of the degree of stenosis in CAG as the gold standard test. Thus, various physiological assessments may also have limitations in their estimation of coronary lesion severity, these would be more accurate to reflect the degree of coronary lesion stenosis theoretically\(^23\) and objectively,\(^24\) and significant correlations were reported among FFR and other physiological assessments\(^74\text{-}77\) including a recent report of correlation between FFR and MRI myocardial perfusion image.\(^77\) Furthermore, in patients with stable CAD and multivessel disease especially, as discussed with regard to anatomical assessment, identification of the culprit stenosis or stenoses could be more accurately and objectively done using FFR or other physiological methods in daily clinical practice, and the number of diseased vessels also would be identified much more correctly and objectively. Moreover, relief of ischemia would also be objectively assessed immediately after treatment if FFR were used as the guide to PCI.\(^78\text{-}79\) and in fact retrospective studies suggest that in patients with multivessel CAD, FFR-guided PCI is associated with a favorable outcome with respect to event-free survival.\(^80\text{-}81\)

**What Can We Expect in PCI?**

As stated, previous data demonstrate an improvement in prognosis only in patients with 3-vessel disease and poor LV function not by PCI but by CABG.\(^45\text{-}47\) Although successful PCI of flow-limiting stenoses might be expected to reduce the rate of death, MI, and hospitalization for ACS, previous studies have revealed only that PCI decreases the frequency of angina and improves short-term exercise performance in patients with stable CAD.\(^22\text{-}23\text{,}36\) Thus, the long-term prognostic effect of PCI on cardiovascular events in patients with chronic CAD remains uncertain.\(^37\) For stenotic lesions without any evidence of inducible ischemia, the benefit of revascularization is unclear, and medical therapy alone is likely to be equally effective.\(^37\text{-}39\)\(^66\text{-}82\) In the DEFER study, although neither BMS nor DES was used in PCI, the possibility of a deterioration in the prognosis of CAD by the performance of PCI is assumed if PCI was performed for a lesion without physiological evidence of ischemia, even if it was anatomically significant.\(^66\text{-}82\) (Figure 1). Furthermore, the limitation of anatomical assessment of stenosis severity by angiography was also described, based on the finding of a discrepancy between physiological lesion assessment by FFR and anatomical assessment by CAG.\(^66\) In patients with stable CAD and multivessel disease in particular, as discussed earlier, the identification of the culprit stenosis or stenoses requires anatomical orientation by angiography in daily clinical practice in the cardiac catheterization laboratory and the number of diseased vessels could be misjudged by qualitative visual assessment in routine clinical practice. Recently, the FAME study revealed that only 63.0% of all lesions in angiographically diagnosed multivessel disease (2- or 3-vessel disease) demonstrated the lesions were physiologically significant, and approximately 35% of lesions do not demonstrate ischemia objectively if FFR is used to identify the significant coronary lesions in an unselected population, not just in persons with intermediate lesions, in clinical practice.\(^39\) Furthermore, in that study, PCI that was physiology-oriented by FFR, as compared with the standard strategy of PCI guided by CAG, significantly reduced the rate of the primary composite endpoint of death, MI, and repeat revascularization at 1 year, and also the combined rate of death and MI\(^39\) (Figure 2).

A substudy of the COURAGE trial, which showed that patients with the greatest relief of ischemia had the lowest rates of death and MI,\(^38\) further supports the concept that PCI should be guided by physiological considerations and not solely by anatomical ones because, as described above, PCI does not have the long-term prognostic effect on cardiovascular outcomes.

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*Figure 1.* Event-free survival in the Defer study. Kaplan-Meier survival curves for freedom from adverse cardiac events during 5 years of follow-up for the 3 groups, Defer, Perform and Reference. Defer group comprised patients who had deferral of percutaneous coronary intervention (PCI) because there was no evidence of ischemia by fractional flow reserve (FFR). Perform group comprised patients who underwent PCI based on angiographic findings without evidence of ischemia by FFR. Reference group comprised patients who underwent PCI because of ischemic FFR.\(^82\)
cular events but only decreases the frequency of angina and improves short-term exercise performance in patients with stable CAD. Thus, in patients with stable CAD and multivessel disease specifically, identification of the culprit stenosis or stenoses requires anatomical orientation by angiography combined with functional evaluation, obtained either by noninvasive imaging before catheterization or during the invasive procedure using pressure-derived FFR measurements, because significant correlations have been demonstrated between the various non-invasive imaging techniques and FFR.

**Can We Expect a Prognostic Effect for PCI With DES on MACE?**

Recently developed DES have dramatically reduced in-stent restenosis compared with BMS, and comparable prognoses were initially expected for PCI with DES compared with CABG. However, meta-analysis of randomized trials has demonstrated no significant differences in the long-term rates of death or MI after DES or BMS use either off-label or on-label, although a marked and comparable reduction in target vessel revascularization with the use of DES compared with BMS has been confirmed. Even among the first-generation DES, however, sirolimus-eluting stents are thought to be superior to paclitaxel-eluting stents in terms of a significant reduction of the risks of re-intervention and stent thrombosis, even though the risk of death is not significantly different between the 2 DES, and no significant differences in the long-term rates of death or MI have been demonstrated for the first-generation DES. As could be speculated, in cases of 3-vessel or LMCA disease in the SYNTAX trial, as compared with PCI, CABG resulted in lower rates of the combined endpoint of major adverse cardiac or cerebrovascular events at 1 year, and no advantages in prognosis for PCI with DES were demonstrated using the paclitaxel-eluting stent. However, the recently developed second-generation DES have demonstrated much lower risks of in-stent restenosis, target lesion revascularization and stent thrombosis, and because the prognosis in Japanese patients after DES implantation is better compared with the reports from USA or Europe, advances in prognosis for PCI with the second-generation DES can be expected. In a Japanese registry, in particular, the unadjusted and adjusted survival outcomes for CABG and PCI with BMS were not significantly different in any subgroups when elderly patients >75 years old were excluded from the analysis. Further randomized studies in Japan comparing CABG and PCI with second-generation DES are required.

**Conclusion**

As discussed, although PCI, performed with DES or BMS, reduces the incidence of death and MI in patients with ACS and also decreases the frequency of angina and improves short-term exercise performance in patients with chronic CAD, its long-term prognostic effect on cardiovascular events, including death and MI, remains uncertain in patients with stable CAD. In conclusion, while the long-term prognostic effect of PCI on MACE has not yet been proved obviously in patients with stable CAD, we should restrain ourselves from performing simple PCI as treatment of lesions with angiographically significant coronary artery stenosis but without any objective evidence of myocardial ischemia, and clinicians should make their ultimate goal not the short-term daily activities of a patients’ life or excellent cosmetic PCI results but rather the improvement of the patient’s prognosis itself.

**Figure 2.** Event-free from major adverse cardiac events (MACE) in the FAME study. Kaplan-Meier survival curves for freedom from MACE during 1-year follow-up for the 2 groups: angiography-guided and FFR-guided percutaneous coronary intervention. FFR, fractional flow reserve.
42. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild
49. Lytle BW, Loop FD, Cosgrove DM, Ratliff NB, Easley K, Taylor
44. Nishigaki K, Yamazaki T, Kitabatake A, Yamaguchi T, Kanmatsuse
51. Barner HB, Barnett MG. Fifteen- to twenty-one-year angiographic
21. Writing Group
40. Emond M, Mock MB, Davis K, Fisher LD, Holmes DR, Chaitman
50. Loop FD, Lytle BW, Cosgrove DM, Stewart RW, Goormastic M,
43. Volpi A, De Vita C, Franzosi MG, Geraci E, Maggioni AP, Mauri
38. Reed JS, Norgren L, Waugh N, Fowkes FG. The transatlantic stroke
54. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial per
22. ACST/SCAI/ST/SIR/SCCT/ASNC/ACR 2004 contrast criteria for
20. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ,


86. Nakamura M. Angiography is the gold standard and objective evidence of myocardial ischemia is mandatory if lesion severity is questionable: Indication of PCI for angiographically significant coronary artery stenosis without objective evidence of myocardial ischemia (Pro). *Circ J* 2011; 75: 204–210.

**Authors’ Comments on the Pro-Side Author**

Although there are limitations to the evaluation of myocardial ischemia in each physiological examination, even with pressure-derived fractional flow reserve (FFR), as Dr Nakamura has pointed out, these limitations should not lead us to the conclusion that the clinician performs PCI for angiographically significant coronary artery stenosis without any objective evidence of inducible myocardial ischemia. Because, as discussed regarding chronic CAD in this article, no advantage in improvement of prognosis for PCI compared with aggressive medical therapy has been reported by previous studies, and for stenotic lesions without evidence of ischemia the benefit of revascularization is less clear at the moment. Furthermore, there is the possibility of a deterioration in the prognosis of CAD treated by PCI if PCI is performed in a lesion without physiological evidence of ischemia, even if it is anatomically significant. Thus, PCI should be limited to significant coronary artery stenosis with objective, inducible myocardial ischemia.