

# Prognostic superiority of coronary artery bypass grafting to percutaneous coronary intervention in non-diabetic patients with anatomically complex multivessel coronary artery disease

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The rationale for revascularization in patients with stable coronary artery disease (CAD) is to improve prognosis and relieve symptoms. Revascularization may be indicated in flow-limiting coronary stenosis to reduce myocardial ischemia and its adverse clinical manifestations especially for patients with multivessel CAD. Currently, both US and European guideline statements recommend coronary artery bypass grafting (CABG) rather than percutaneous coronary intervention (PCI) for patients with multivessel CAD (1,2). This recommendation is based primarily on the pivotal Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial, which randomized 1,800 patients with extensive angiographic left main and 3-vessel CAD to either PCI with first-generation stents, paclitaxel-eluting stents, or CABG (3). The SYNTAX trial showed significantly higher rates in achieving the primary endpoint, which was defined as a composite of major adverse cardiac and cerebrovascular events (MACCEs) including death, myocardial infarction (MI), stroke, and repeat revascularization, in the PCI group at 1 year. By 5 years, these results showed a more significant separation between CABG and PCI groups for cardiac death, MI, repeat revascularization, and MACCEs, which were all significantly in favor of the CABG group (4). Within the 3-vessel CAD subgroup, in patients with a low SYNTAX score ( $\leq 22$ ), which is a novel score for anatomical assessment derived from lesion severity and complexity, the incidence of cardiovascular outcome was similar

between the PCI group and CABG group. However, in the intermediate SYNTAX scores [23–32] and high SYNTAX scores ( $\geq 33$ ), the incidence of a composite of the MACCEs was significantly higher in the PCI group than in the CABG group. This difference was primarily driven by a higher incidence of repeat revascularization.

Although first-generation drug-eluting stents (DESs) reduced the rate of restenosis, their use was associated with a relatively high rate of stent-related thrombotic events. A first-generation DES was used in the SYNTAX trial, and clinical events occurring in the PCI group were associated with stent thrombosis (5). The BEST trial (6) was a randomized clinical trial involving patients with multivessel CAD in which CABG was compared with PCI with the use of newer, second-generation everolimus-eluting stents, which reduced the rate of death, MI, restenosis, and stent thrombosis compared with first-generation DESs (7-9). The trial was an undersized randomized trial because it was terminated according to slow enrollment. The trial showed that the primary composite endpoint, including death, MI, or target vessel revascularization was similar between CABG and PCI at 2 years, although there were significantly fewer MIs and target vessel revascularizations in CABG compared with PCI during the longer period of 4.6 years. However, these trials were not powered to detect a small difference in all-cause mortality.

Although CABG leads to lower MACCE rates in

contemporary RCTs and meta-analyses for patients with multivessel CAD treated with CABG or DESs, this advantage is driven mainly by a reduction in the rate of repeat revascularizations, which is considered a soft endpoint by many physicians and patients wishing to avoid more invasive cardiac surgery compared with PCI in clinical settings. Therefore, data on the risk of death, MI, and stroke will clearly influence decision making in treatment options for patients with multivessel CAD. Additionally, there is little evidence regarding the optimal revascularization strategy in non-diabetic patients with multivessel CAD. Therefore, to address this challenging problem, Chang *et al.* (10) in the issue of the *Journal of The American College of Cardiology*, presented a few insights from a patient-level pooled analysis regarding the mortality benefit in non-diabetic subgroups of the SYNTAX and the BEST trials, databases from two randomized trials were merged to overcome the power limitation of the individual studies. In that study, the median length of follow-up after randomization was 61 months. The primary outcome of death from any cause was significantly lower in the CABG (6.0%) compared with the PCI (9.3%) group [hazard ratio (HR): 0.65; 95% confidence interval (CI): 0.43 to 0.98;  $P=0.039$ ]. In patients with low SYNTAX scores, the two strategies were comparable with respect to mortality (6.0% in CABG *vs.* 7.5% in PCI, log-rank  $P=0.662$ ), but in those with intermediate or high SYNTAX scores, CABG was distinctly superior to PCI with DES (7.1% *vs.* 11.6%, log-rank  $P=0.023$ ). The rate of MI was significantly lower after CABG than after PCI (HR: 0.40; 95% CI: 0.24 to 0.65;  $P<0.001$ ). The need for repeat revascularization was significantly lower in the CABG group than in the PCI group (HR: 0.55; 95% CI: 0.40 to 0.75;  $P<0.001$ ). However, the rate of stroke was not different between the two groups (HR: 1.13; 95% CI: 0.59 to 2.17;  $P=0.714$ ).

From these results of the patient-level pooled analysis, should CABG be considered as a superior revascularization strategy to PCI in non-diabetic patients as well as in diabetic patients with multivessel disease? To interpret these results properly, several uninvestigated issues should be mentioned. When mortality is discussed in this patient cohort, it is important to consider specific causes of death after both revascularization options for multivessel CAD. Causes of death following PCI *vs.* CABG in complex CAD from 5-year follow-up of the original SYNTAX trial were reported. In the CABG group, 49.4% of deaths were cardiovascular, with the greatest cause being heart failure, arrhythmia, or other causes (24.6%), whereas in

the PCI group, the majority of deaths were cardiovascular (67.5%) and as a result of MI (29.3%) during a 5-year follow-up (11). These results indicated that treatment following PCI should target reducing post-revascularization spontaneous MI. Furthermore, when the cause of post-revascularization spontaneous MI was explored in more detail, several unresolved issues in the study emerged.

Firstly, a higher frequency of angiographically incomplete revascularization was reported in patients treated by PCI than by CABG (the ratio of complete revascularization; PCI 56.7% *vs.* CABG 63.2%,  $P=0.005$ ) in the original SYNTAX trial (3). Angiographically incomplete revascularization was associated with an increased risk of MI, repeat revascularization (12), and cardiovascular death (13,14). Moreover, angiographically incomplete revascularization was an independent predictor of mortality only in the PCI group while in the CABG group angiographically incomplete revascularization did not increase the risk of death or cardiac adverse events. In general, diffuse, long, calcified, tortuous, chronic occluded, aortic ostial, bifurcated, and trifurcated lesions were frequently observed in multivessel disease, which made the SYNTAX score high, following possibly angiographically incomplete revascularization in patients with multivessel CAD in the PCI group. This anatomically incomplete revascularization may have contributed to the worse outcomes in the PCI group.

Secondly, in both the SYNTAX and BEST trials included in that study, angiography-guided PCI was performed and may be a more disadvantageous strategy compared to CABG. Reducing ischemia in patients with stable angina pectoris is strongly associated with the prognosis. However, angiography-guided PCI sometimes miss the necessary revascularization for lesions with functional ischemia because of anatomical intermediate or mild stenosis, resulting in functionally incomplete revascularization. On the other hand, angiography-guided PCI may cause unnecessary revascularization for lesions without functional ischemia because of anatomically severe stenosis, which may cause procedure-related MI post procedure and late stent thrombosis and neoatherosclerosis in the future.

Thirdly, in terms of plaque assessment in patients after PCI, the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study showed that future MI-related events after PCI occurred not only in severe stenotic lesions (a plaque burden of 70% or greater or a minimal luminal area of 4.0 mm<sup>2</sup> or

less) and vulnerable plaque (radiofrequency intravascular ultrasonography derived thin-cap fibroatheromas) in culprit vessels, but also in non-culprit vessels (15). In that study, patients treated with PCI were not protected against adverse events because angiography-guided PCI as a local treatment for an anatomically severe stenotic lesion does not target anatomically intermediate or mild stenosis with vulnerable plaque in the culprit vessel as well as in non-culprit vessels. Therefore, the angiography-guided PCI in that study, which included pooled data from two trials, was nothing more than local anatomical treatment, and gave little thought about reducing the ischemia and prevention of future rupture-prone plaque. Furthermore, the PROSPECT sub-analysis suggested that there were no significant differences in vulnerable plaque phenotype, such as radiofrequency intravascular ultrasonography derived thin-cap fibroatheromas, in non-culprit lesion between diabetes and non-diabetes, whereas diabetic patients, compared with those with normal cardiometabolism, were more likely to have the ratio of anatomically severe stenotic lesion, such as plaque burden >70% and minimum lumen area <4.0 mm<sup>2</sup> (16). From these findings, these problems seem to be enhanced especially in multivessel CAD compared with one vessel CAD even in non-diabetic patients. On the other hand, CABG targets angiographically significant lesions, and also provides protection from less severe stenotic lesions with functional ischemia and/or less severe stenotic lesions with rupture-prone vulnerable plaque as well. Thus, in that study, CABG had an advantage in the reduction of myocardial ischemia and in the avoidance of MI caused by a coronary event in the bypassed segment, which may explain that CABG is superior to PCI in preventing future coronary events resulting from MI. These benefits may emphasize, especially in patients with 3-vessel disease, in favor of protection of all three coronary arteries. Although the detection of ischemia is crucially important in deciding the indication for revascularization, myocardial perfusion imaging (MPI) performed by single-photon emission computed tomography has been shown to have sub-optimal accuracy in detecting multivessel CAD. Therefore, fractional flow reserve (FFR) by using a pressure wire is more appropriate for detecting myocardial ischemia in multivessel CAD accurately compared with MPI (17,18). The ongoing FAME 3 trial (NCT02100722) aims to randomly assign 1,500 patients to FFR-guided PCI with second-generation DESs or CABG to show the non-inferiority of FFR-guided PCI compared with CABG in patients with multivessel CAD. This trial will provide some

evidence of the efficacy of FFR-guided PCI in patients with multivessel CAD; however, FFR-guided PCI cannot avoid a spontaneous MI derived from vulnerable plaque without functional ischemia. Recently, the impact of optimal medical therapy (OMT), defined as the combination of at least one antiplatelet drug, statin,  $\beta$ -blocker, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, on clinical outcome in complex CAD from a 5-year follow-up of the original SYNTAX trial was reported (19). This sub-analysis showed that the use of OMT remains low in patients with complex CAD requiring revascularization. Moreover, OMT was an independent predictor of survival and was associated with a significant reduction in mortality and the composite endpoint of death/MI/stroke at the 5-year follow-up. The treatment effect of OMT was greater than the treatment effect of revascularization strategy. In that study, all the components of OMT were important for reducing adverse outcomes, and similar magnitude of benefit was observed regardless of diabetic status. From these findings, even though blood flow was restored, these patients had a substantial atherosclerotic burden and remain at risk for future ischemic events, and the use of OMT can play an important role in reducing this risk. Therefore, OMT should be considered for all patients with complex CAD treated with medical therapy, PCI, or CABG unless contraindicated.

On the basis of currently available evidence, CABG is the reasonable revascularization modality of choice for non-diabetic patients with multivessel disease as well as for diabetic patients. At least, PCI can be considered a valid option for selected low-risk (low SYNTAX score) patients with multivessel CAD regardless of assessment of functional ischemia and vulnerability. Further studies focused on the assessment of functional ischemia and lesion vulnerability as well as medical intervention are warranted to clarify an even more appropriate strategy to improve the prognosis for patients with functional and vulnerable multivessel CAD.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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