Percutaneous or surgical revascularization in multivessel coronary artery disease: synthesis from SYNTAX

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This editorial refers to ‘Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final 5-year follow-up of the SYNTAX trial’, by S.J. Head et al., on page 2821

In the current issue of the journal Head and colleagues present the 5-year outcome of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in the cohort of SYNTAX patients with three-vessel coronary artery disease (CAD). They report a number of important clinical findings, of which the most significant is that CABG offered a marked reduction in absolute mortality (by 5.4%), myocardial infarction (by 7.3%), and the need for repeat revascularization (by 12.8%). The benefits of CABG increased with increasing complexity of CAD so that the survival advantage increased to 9% in those with the most severe disease. These benefits were further magnified in patients with diabetes where the overall absolute reduction in mortality was 10.1%. Finally, as the MACCE (major adverse cardiac and cerebrovascular event) curves, including survival, continue to diverge at 5 years, this implies that these intermediate term results may actually underestimate the real benefits of CABG over an even longer term.

These findings are dramatic and raise three important questions. First, are the results likely to be real? Secondly, why are the results so different from the findings in most previous trials of PCI and CABG? Thirdly, are the results likely to be altered by newer generation stents with proven superior performance and safety?

Before answering these questions, it should be acknowledged that the SYNTAX trial is unquestionably the most important randomized trial of PCI and CABG ever to have been conducted, and the investigators should be congratulated on this outstanding achievement. It is, however, also important to recognize some obvious potential weaknesses of the study of Head et al. As the primary endpoint of non-inferiority of PCI for all SYNTAX patients in the SYNTAX trial was not met, then further subset analyses can only be considered as ‘hypothesis generating’. Also the numbers of patients in each tercile of SYNTAX scores was relatively small. In addition, as discussed below, critics will also argue that in the PCI cohort stent technology was relatively crude in comparison with today’s standards.

Accepting these caveats, reassurance that the current results of SYNTAX are likely to be real comes from the findings of a meta-analyses of six recent trials of PCI vs. CABG with 6054 patients that reported a hazard ratio for mortality with CABG of 0.73 (95% confidence interval 0.62 – 0.86; \( P < 0.001 \)) as well as a 40% reduction in the subsequent incidence of myocardial infarction and a 70% reduction in the need for repeat revascularization. Additionally, several large propensity-matched registries of patients with CAD have also consistently reported a similar survival advantage of CABG over PCI. While the major strength of such registries is that they contain tens of thousands of patients and represent routine clinical practice, their major potential weakness, in the absence of randomization, is the possibility of confounding by biases, both known and unknown. Nevertheless, these registries have not only uniformly and consistently demonstrated a similar magnitude of survival advantage for CABG over PCI at 5 years in patient cohorts comparable with those reported in SYNTAX but also a similar continuing divergence of survival curves at 5 years, again emphasizing that this time point may be still too early to quantify the real benefit of CABG over the longer term. Similarly, the survival benefit of CABG in patients with diabetes in the SYNTAX trial is supported by both the FREEDOM trial and two independent meta-analyses. Why then are the results of the SYNTAX trial in patients with three-vessel CAD so strikingly at odds with the results of most previous trials of PCI and CABG that reported no difference in survival between the two interventions? The most likely explanation is simply the differing nature of the patient populations included in SYNTAX and the previous trials. In marked contrast to earlier trials, which only recruited ~ 5% of the totally eligible population, SYNTAX

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was a relative ‘all comer’ trial. (However even in SYNTAX we do not know the real total potentially suitable population but rather only those who were screened.) Furthermore, the vast majority of patients in previous trials also had low severity CAD (around two-thirds of patients actually had one- or two-vessel disease and only 40% had proximal left anterior descending CAD), where it would be difficult to demonstrate a survival advantage of any revascularization strategy in comparison with medical therapy. In contrast, a high proportion of SYNTAX patients had left main and/or three-vessel CAD. A further major strength of SYNTAX was its inclusion of a nested parallel registry to capture outcomes in patients deemed ineligible for randomization (the vast majority of whom had disease of such complexity that it was considered only suitable for treatment by CABG).

Most crucially, the survival benefit of CABG over PCI in three-vessel CAD is unlikely to be altered by newer generations of stents. Over the last two decades from balloon angioplasty to bare metal and then drug-eluting stents, the constant retort of the interventional cardiologist, to inferior results with PCI in comparison with CABG, has always been ‘but now we have a new stent’ and implying that earlier results can be considered historically irrelevant. However, this underlines a lack of clarity in understanding both the pathophysiology of CAD and the different effects of CABG and PCI. CAD is a chronically progressive disease that predominantly affects the proximal coronary arteries. The most likely reason for the survival benefit of CABG over PCI is that the placement of bypass grafts to the mid coronary vessel not only makes the complexity of proximal CAD lesions irrelevant but over the longer term also offers prophylaxis against the development of new proximal disease. In contrast, the early success of PCI is inversely correlated to the complexity of the proximal lesion, while its longer term benefit can be negated by the development of new CAD. This is clearly evidenced in the report of Head et al.1 where CABG prevents the annual increase in the incidence of myocardial infarction observed after PCI. Consequently, simply changing the nature of the stent cannot offer the prophylactic benefit of bypass grafts. Furthermore, and in particular, it has been recognized for almost three decades that high rates of nitric oxide production from the internal mammary artery (IMA) graft protects the native coronary circulation from further disease development (Figure 1). Accordingly, in the SYNTAX trial, it is disappointing that only 30% of patients received bilateral IMA grafts despite the fact that they can be used with a consistently low operative mortality and their documented longer term survival benefits. However use of bilateral IMA grafts in 30% of SYNTAX patients is still superior to the truly lamentable fact that < 10% of patients undergoing CABG in Europe and < 5% in the USA receive this therapeutic option.

Head et al. also address the differing effects of incomplete revascularization in the CABG and PCI cohorts. While incomplete revascularization did not significantly affect overall MACCE at 5 years in the CABG group it did result in a significant increase in the PCI group (43% vs. 33%). This can be explained by understanding the difference in ‘appropriate’ and ‘inappropriate’ incomplete revascularization. The latter scenario occurs when PCI fails to treat large vessels with complex proximal lesions effectively or to re-open chronic total occlusions subtending large areas of viable myocardium, thereby leading to adverse outcomes. However, such a scenario is rare during CABG where the complexity of proximal lesions is irrelevant and when large vessels with proximal occlusions would always be revascularized. In contrast, the decision not to graft small coronary arteries (< 1.25 mm diameter) during CABG is appropriate and of unlikely adverse functional significance.

With regards to stroke, there was no significant difference in its incidence between PCI and CABG in patients with three-vessel CAD, consistent with the findings in a contemporary meta-analyses of randomized trials of PCI vs. CABG. It is notable that there is a higher incidence of stroke at the time of intervention for CABG but not PCI, but a later ‘catch up’ incidence of stroke in the PCI group mitigates this difference. This is somewhat counter-intuitive as the PCI group are maintained on more optimal medical therapy than the CABG group. Furthermore there is strong evidence that an off-pump CABG technique avoiding any manipulation of the aorta can also significantly reduce the incidence of stroke. In the SYNTAX trial, off-pump surgery was only used in 14% of patients and what proportion was performed with a no-touch aortic technique is not specified.

Although not addressed in the study of Head et al., another key observation is that the results for the subset of patients with three-vessel CAD are different from those in the subset with left main disease in whom there was no survival advantage of CABG but a higher risk of stroke. It is possible that in patients with lower severity left main disease, particularly ostial and midshaft lesions, but without additional proximal CAD, there is too much competitive flow for bypass grafts.

Even accepting the caveats about subset analyses, the SYNTAX trial is, unequivocally, the most comprehensive, ambitious, and insightful trial of the effects of PCI and CABG in patients with complex CAD. The results of SYNTAX have reversed the previous widely held dogmas that most three-vessel CAD can be as effectively treated by PCI as CABG and that left main disease should be reserved solely for the domain of surgery. Consequently, SYNTAX has rightfully played a key role in the guideline recommendations for PCI and CABG both in Europe and in North America, and will profoundly influence and guide interventions in complex CAD for the foreseeable future. Although not discussed in the study of Head et al., the SYNTAX trial also reintroduced the concept that patients with

![Figure 1](image-url)
complex CAD should have recommendations for intervention discussed by the multidisciplinary or ‘heart team’ rather than an individual practitioner. This is without doubt the single, simplest, safest, and surest way to reduce inappropriate interventions in stable CAD and, most importantly, to ensure that doctors collectively recommend—and that patients receive—the optimal treatment. This may be, arguably, the greatest legacy of the SYNTAX trial.

Conflict of interest: none declared.

References