Five years after the SYNTAX trial: what have we learnt?

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Keywords: Coronary artery bypass grafting • Percutaneous intervention • SYNTAX study • Left main stenosis • Multivessel disease

Ever since the advent of percutaneous intervention (PCI) for the treatment of coronary artery disease (CAD), the optimal choice of therapy (PCI or coronary artery bypass grafting [CABG]) has always been disputed. Although previous multicentre randomized trials, like the ARTS I, MASS II and SoS trials for multivessel disease (MVD) have shown no compelling benefit in terms of 5-year all-cause and cardiac mortality for CABG, they have consistently reported significantly greater rates of repeat revascularization for PCI [1–3]. Contrary to this, the 5-year follow-up results of the SYNTAX trial for the whole randomized cohort not only confirmed that CABG is associated with lower rates of repeat revascularization (13.7% for CABG vs 25.9% for PCI [P < 0.0001]), but also demonstrated a significant benefit in cardiac mortality (5.3% for CABG vs 9% for PCI [P < 0.003]), occurrence of major cardiac and cerebrovascular events (MACCEs; 26.9% for CABG vs 37.3% for PCI [P < 0.001]) and myocardial infarction (MI; 3.8% for CABG vs 9.7% for PCI [P < 0.001]) in patients undergoing CABG. The rates of all-cause mortality and stroke, however, were not significantly different between groups [4].

What has made the SYNTAX trial exclusive from previous ones was that more than two-thirds of the patients (n = 3075, 71%) screened were recruited, either in the randomized (n = 1800) group, when eligible, or in the PCI and CABG nested registries (n = 1275), when not suitable for randomization, thus reflecting real-world practice [5]. As a result, the major criticism of previous trials, which was the exclusion of patients encountered in the ‘real-world scenario’, was overcome. The results of the SYNTAX trial are in accordance with the recently published ASCERT study, which is an analysis of large non-randomized observational data from the Society of Thoracic Surgeons and American College of Cardiology Foundation registries to evaluate the effectiveness of revascularization with CABG compared with PCI. The adjusted 4-year mortality was 16.4% in the CABG group and 20.8% in the PCI group (risk ratio, 0.79; 95% confidence interval, 0.76–0.82) [6]. Secondly, it is the largest trial that compared CABG using the latest techniques (arterial grafts) with PCI with drug-eluting stents (DESs). Thirdly, a heart-team approach, involving a local interventional cardiologist and a cardiothoracic surgeon supported by a study coordinator at each site, was applied to assess the suitability of patients for either treatment. Finally, it incorporated patients with complex CAD, including left main disease (LMD) and three-vessel disease (3VD), which formed two of the three predefined subgroups analysed. Since the primary clinical endpoint of the trial, which was freedom from MACCE at 1 year after allocation, failed to demonstrate non-inferiority of PCI to CABG, further subgroup analysis can only be considered observational and hypothesis-generating [7]. The 5-year MACCE rates were not significantly different between treatment groups (31.0% CABG vs 36.9% PCI; P = 0.12) in the overall LMD subgroup. In contrast, patients with 3VD and without LMD had 50% greater 5-year MACCE rates when treated with PCI compared with CABG (24.2% CABG vs 37.5% PCI; P < 0.001). Medically treated diabetic patients (third subgroup), who underwent CABG, also had lower 5-year MACCE rates (29.0% CABG vs 46.5% PCI; P < 0.001), which was comparable with the primary composite outcome of death from any cause, MI and stroke in diabetic patients included in the FREEDOM trial (18.7% CABG vs 26.6% PCI; P = 0.005) [8].

The trends of various outcomes of the SYNTAX trial are depicted in Tables 1 and 2. Notably, the composite outcome of death, MI and stroke achieved significance in favour of CABG for the first time at 5-year follow-up. This was chiefly driven by the significantly lower rates of cardiac death and MI in CABG-treated patients and the levelling out of the stroke rate between the two treatment groups at 5 years. This long-term benefit seen with CABG is due to the fundamental difference in the method of revascularization. Bypass grafts are anastomosed to coronary arteries distal to the lesions, thus rendering the complexity of the lesion inconsequential and providing an adequate buffer against the development of new lesions in the future. Since the source or inflow of bypass grafts is different from that of native coronary arteries, the development of new lesions proximal to the anastomoses is impertinent. In contrast, stents have to be deployed at the site of the lesion, which provides no protection against the progression or development of new disease, as the native coronary artery always remains the source of inflow.

The CABG registry consisted of patients ineligible for PCI, i.e. usually those with highly complex or diffuse CAD. The MACCE (23.2%), all-cause death (12.6%), MI (3.8%) and repeat revascularization (6.7%) rates at 5 years in these patients were consistent with those in the randomized CABG arm. This would further enforce the fact that CABG results are not really dependent on the complexity of CAD anatomy. The PCI registry included patients who were considered to be at high risk for CABG, probably due to severe multiple comorbidities, poor ventricular function, etc. This probably explains the poorer outcomes (MACCE: 42.9%, all-cause death: 35.5% and death/stroke/MI: 35.3%) of patients in the PCI registry.
What have we learnt from the SYNTAX trial after 5 years?

1. The five-year results of the SYNTAX trial suggest that 63% of all patients are still best treated with CABG; these include patients in the CABG registry (n = 644) and in the randomized trial (LMD and 3VD with SYNTAX score ≥33 [n = 605] and 3VD with SYNTAX score 23–32 [n = 415]). Only 7% of patients would probably be best treated with PCI (PCI registry). For the remaining 30% of patients, PCI can be, at best, only an alternative to surgery (LMD and 3VD with SYNTAX score ≥22 [n = 574] and LMD with SYNTAX score 23–32 [n = 195]).

2. CABG is the treatment of choice for intermediate and complex 3VD, and the complexity of the disease does not seem to have much bearing on the short- or long-term results of CABG. The 5-year outcomes of CABG-treated patients in the trial (all three SYNTAX score tertiles) and in the registry appear to be quite consistent.

3. The beneficial effects of surgery become more evident as we move away from the procedure.

   a. The significantly higher stroke rate observed at 1 year after CABG gradually levelled out with the PCI arm over 5 years. Thus, if future efforts are directed towards reduction in perioperative stroke rates, it would further improve MACCE rates in patients undergoing CABG. Performing off-pump CABG with minimal or no manipulation of the ascending aorta is associated with significantly lower stroke rates and would be a good option to overcome the problem of perioperative stroke [9].

   b. MI rates, which were similar in both treatment arms after 1 year, became significantly higher in the PCI arm after 3 and 5 years.

   c. The composite endpoint of death, stroke and MI achieved significance in favour of CABG for the first time at 5 years.

4. There was no difference in MACCE rates between the two treatment groups in patients with LMD with low-to-intermediate-risk SYNTAX scores. The ongoing EXCEL (Evaluation of Xience Prime vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial, in which more than 2500 patients presenting with unprotected LMD will be randomized either to PCI using an everolimus eluting coronary stent or to CABG, will be able to resolve what the best treatment strategy would be for these patients.

5. Repeat revascularization rates were significantly higher in the PCI arm, not only in the overall group, but also in all the three SYNTAX score tertiles. Thus, in-stent restenosis leading to repeat revascularization in MVD still remains an unsolved problem even in the DES era, which should be a major cause for concern for interventional cardiologists. A pooled analysis of >6000 patients in seven contemporary DES trials showed stent generation (newer generation vs first generation) not to be a predictor of mortality [10].

Thus, the SYNTAX trial has revolutionized decision-making in patients with multivessel CAD by introduction of the SYNTAX score, a heart-team approach and evolving a close cooperation between both cardiac surgery and interventional cardiology, which is reflected in the published ESC/EACTS guidelines on revascularization [11]. Risk stratification based on scores developed by integrating the SYNTAX score with important clinical variables (logistic Clinical SX Score, SYNTAX II score and Global Risk Approach) to aid in determining the optimal revascularization modality in patients with complex coronary disease is on the horizon [10, 12, 13].

**Funding**

The SYNTAX trial was funded by Boston Scientific Corporation. Friedrich W. Mohr was one of the Principal Investigators of the SYNTAX trial.

**REFERENCES**


