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Lessons from the trials

PCI versus CABG in patients with complex coronary artery disease: Time for reconciliation?

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INTRODUCTION

Final 5-year results of the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial were recently presented at the Transcatheter Cardiovascular Therapeutics (TCT) and European Society of Thoracic Surgery (ESTS) meetings [1]. SYNTAX is frequently quoted as “the most important percutaneous coronary intervention (PCI) vs. coronary artery bypass grafting (CABG) trial in multivessel and/or left main (LM) coronary artery disease (CAD) conducted to date” [2,3] However, the impact of its findings on day-to-day clinical practice remains surprisingly humble [4].

DISCUSSION

SYNTAX was a randomized “all-comers” multicenter trial conducted in 85 centers across Europe and the United States designed to test the hypothesis that PCI with paclitaxel drug eluting stents (DES) is non-inferior to CABG in patients with 3-vessel and/or LM coronary artery disease. The trial randomized 1800 patients judged to be eligible for either strategy to CABG (n = 897) or PCI (n = 903). Patients who were deemed ineligible for CABG or ineligible for PCI were entered into one of two “nested” registries.

Eligibility was jointly determined by a cardiothoracic surgeon and interventional cardiologist belonging to the “Heart Team”.

The decision was aided by the SYNTAX score - a novel grading system based on the patient's coronary anatomy that was developed for the trial [5]. Accordingly, 1077 patients were deemed ineligible for PCI and entered into the CABG registry and 198 patients were deemed ineligible for CABG and entered into the PCI registry. The primary clinical end-point was the composite of Major Adverse Cardiac and Cerebrovascular Events (MACCE) (all-cause mortality, cerebrovascular accidents, nonfatal myocardial infarction and repeat revascularization at 12 months). A co-primary safety end-point was the composite of all-cause mortality, cerebrovascular accidents and nonfatal myocardial infarction.

Secondary end-points included MACCE at 6 months, 3 and 5 years as well as individual components of the composite primary end-point. Secondary end-points also included quality of life at one month post procedure and at 6 months, 1, 3 and 5 years post allocation as well as cost and cost-effectiveness at 1, 3 and 5 years. The study missed its primary end-point with PCI failing to prove non-inferior to CABG at 12 months [2].

At 5 years, patients with multivessel disease who underwent CABG had fewer MACCE compared to those who underwent PCI [24.2% (n = 133) vs. 37.5% (n = 205), $p < 0.001$]. Importantly, a similar difference was noted in two of the individual components of the composite end-point with fewer deaths and myocardial infarctions occurring in the CABG group compared to PCI: all-cause mortality [9.2% (n = 50) vs. 14.6% (n = 80), $p = 0.006$] and non-fatal myocardial infarction [3.3% (n = 18) vs. 10.6% (n = 58), $p < 0.001$]. A more pronounced difference was observed in cardiac mortality [4% (n = 22) in the CABG group vs. 9.2% (n = 50) in the PCI group, $p < 0.001$].

The increased incidence of cerebrovascular accidents (CVA) in the CABG group initially observed at one and three years has leveled out by 5 years to become statistically insignificant [3.4% (n = 19) vs.

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3% (n = 16), p = 0.66)]. The composite safety endpoint of death, CVA and MI also fell significantly in favor of surgery [14% (n = 77) vs. 22% (n = 120), p < 0.001]. Patients undergoing PCI had significantly higher rates of repeat revascularization compared to CABG [12.6% (n = 69) vs. 25.4% n = 139, p < 0.001]. PCI was however shown to be equally safe to CABG in patients with a low SYNTAX score (<22), but at the cost of a higher rate of repeat revascularization. This group comprised only 20% of the SYNTAX population.

On the other hand, patients with left main disease showed no significant difference in outcome between both strategies apart from a higher incidence of repeat revascularization in the PCI group compared to CABG [26.7% (n = 95) vs. 15.5% (n = 54), p < 0.001] albeit with a lower incidence of cerebrovascular accidents [1.5% (n = 5) vs. 4.3% (n = 15) p = 0.03]. Subgroup analysis showed that PCI in patients with low and intermediate SYNTAX scores (<33) had comparable outcomes to CABG particularly in those with isolated left main and/or left main plus single vessel disease.

The trial comprises several unique features that render it the wealthiest source of evidence in patients with multivessel and/or LM disease:

1. With 1800 patients and 85 participating centers, SYNTAX is the largest randomized study comparing PCI vs. CABG.
2. It is a true “all-comers” trial with exclusion criteria being limited to previous revascularization, acute MI or need for concomitant surgery. Of the 4337 patients screened, 3075 were eventually recruited to the trial or one of its nested registries (71% enrollment rate). This is in contrast to the highly selected patient populations enrolled in similar previous studies (only 5–10% enrolment rate).
3. Contrary to previous trials where the techniques used were usually outdated by the time the results were published, findings from SYNTAX remain very much valid today. The trial utilized state-of-the-art revascularization techniques in both treatment arms: bilateral internal thoracic arterial grafting was used in 27.6% of patients and 18.9% received total arterial revascularization in the CABG group. Similarly, all patients in the PCI group received DES. Both groups received near-optimal medical treatment.
4. The use and validation of a novel semi-quantitative anatomical risk-stratification tool – the SYNTAX score – to grade the severity and complexity of coronary artery disease in individual patients rather than relying on the existing clinical risk scores used in all other trials.
5. SYNTAX is often considered the first “real-life” application of the multidisciplinary Heart Team concept. Clinical and angiographic data of every patient were reviewed simultaneously by an interventional cardiologist and surgeon who reached a consensus on which revascularization strategy(s) the patient was eligible for.

The pitfalls in the trial were limited and unlikely to alter the overall conclusions:

1. The use of second generation DES might have decreased the abnormally high incidence of stent thrombosis seen in the PCI group (3.3%).
2. The initially observed increased risk of stroke in patients who underwent CABG might have been reduced markedly with more liberal use of bilateral internal mammary arteries and off-pump coronary artery bypass. Utilizing the “no-touch” technique has decreased the incidence of stroke to less than 0.3% with CABG in some centers.
3. Despite strong recommendations in recent practice guidelines, [6], the SYNTAX scoring system is still being perceived as a labor-intensive exercise with fair reproducibility [7]. This has markedly limited its wide-spread adoption in daily clinical practice.
4. Risk stratification of patients in SYNTAX relied solely on anatomical features. The adoption of a more holistic risk stratification score that accounts for clinical risk predictors in addition to angiographic features would have almost certainly enhanced the accuracy of the SYNTAX score [8,9]

WHAT HAVE WE LEARNED?

Despite being – in strict technical terms – a negative trial, SYNTAX offers invaluable insights into the outcomes of different revascularization strategies in patients with multivessel and/or LM disease. CABG remains the revascularization strategy of choice for the majority of patients with multivessel coronary artery disease. PCI might be an equally safe alternative for a small subset of these patients, namely those with SYNTAX scores <22. Left main disease can be safely and effectively treated by PCI in a considerable number of patients (SYNTAX scores <33), particularly those with isolated LM or

LM + single vessel disease. The SYNTAX score is a reasonable semi-quantitative surrogate for the severity and complexity of CAD – factors which should be taken into consideration when making decisions about the optimal revascularization strategy for individual patients.

Genuine implementation of the Heart Team concept is arguably the most valuable lesson learned from the SYNTAX trial. With many remaining uncertainties and countless clinical scenarios, the best outcomes seem to depend profoundly on a multidisciplinary decision-making process aided by quantitative reproducible risk-prediction algorithms. The value of the Heart Team approach in patients with complex coronary artery disease is further addressed in this issue of the journal which also provides valuable insight into the role of SYNTAX in shaping the current practice guidelines [10,11]

The Excel Study (ClinicalTrials.gov identifier: NCT01205776) is expected to provide further answers on the safety and effectiveness of PCI - using second-generation DES - compared to surgery in patients with LM disease.

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