SYNTAX Trial: analysis and clinical implications

Estudo SYNTAX: análise e implicações clínicas

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The SYNTAX trial, presented in the congresses of the European Society of Cardiology in Munich, Germany and the European Association of Cardiothoracic Surgery in Lisbon, Portugal in September 2008, is the first study to compare the clinical results of the best technology of percutaneous coronary interventions (PCI) using pharmacological stents (paclitaxel-eluding stent – Taxus, Boston Scientific Corp) with the best therapy currently provided by coronary artery bypass surgery (CABG) in patients with triple vessel coronary artery disease and/or lesions of the left coronary artery trunk.

The study, carried out in 62 European and 23 American centers and financed by the Boston Scientific Corporation, the manufacturer of the Taxus stent, at a cost of approximately 50 millions US dollars, intended to demonstrate the hypothesis that the PCI-Taxus stent was not inferior to CABG in patients with triple vessel disease and/or lesions of the left coronary artery trunk.

The primary objective of the study was to analyze the compound clinical outcome constituted of death by any cause, strokes, myocardial infarction, the necessity of repeated revascularization by PCI and/or CABG (defined as MACCE - Major Cardiovascular or Cerebrovascular Events) at 12 months of follow up.

Two types of study were formed, the first was randomized and the other was a register. The randomized study included patients that were eligible for both types of procedure (by consensus between the heart surgeon and the hemodynamicist). On the other hand, the register included patients that were considered only eligible for one of the two treatments.

A total of 3075 patients were enrolled, with 1800 presenting with the inclusion criteria for the randomized study; 897 in the CABG Group and 903 in the PCI/Taxus Arm. The other 1275 patients formed the SYNTAX register, where the criterion was that only one treatment method was possible. Thus, 1077 patients were allocated to the Surgery Group and 198 to the PCI Group.

The final result of the SYNTAX trial confirmed that CABG is better than PCIs with drug-eluting stents for this population of high-risk patients. In 12 months, 17.8% of the patients in the PCI/Taxus Group presented with the compound outcome versus 12.1% of the surgical patients with a statistically significantly difference ($p = 0.0015$).

Thus, an analysis of the SYNTAX trial is important not only because of the result but also for the implications of the findings.

Initially, as it was an "all comers" type study enabling the inclusion of patients with characteristics closer to the real world population, instead of being a classical controlled randomized study with many exclusion criteria, it reflected the current clinical practice.

Type of study

This non-inferior trial, which used predefined margins of non-inferiority, attempts to determine that a new treatment is not inferior to the reference treatment. Thus, the results show that the new method is 'slightly' inferior to the standard treatment. The null hypothesis of equality does not apply to this type of test.

Nuances in statistical aspects of non-inferior studies have been the source of criticism. When this type of statistical method is combined with the use of several compound outcomes and different classifications of adverse events, non-inferiority studies are viewed with caution [1,2].

Mortality

The mortality rate at 12 months was 4.3% in the PCI Group and 3.5% in the Surgical Group. The study was not designed and did not have statistical power to analyze differences in isolated outcomes. Nevertheless surgery showed a strong tendency of improved survival over one year, with a 23% benefit in respect to death compared to PCI. This data is consistent with other studies of drug-eluting stents versus CABG, such as the analysis of the New York State register that demonstrated a significant advantage of survival of CABG versus drug-eluting stents over 18 months. This study identified a 21% relative benefit in patients with triple vessel lesions and 35% relative benefit in patients with lesions of two vessels [3].

A further evaluation that will occur after five years will be important. Data of the SCAAR (Swedish Coronary Angiography and Angioplasty Registry) study demonstrated that mortality and myocardial infarction increased between six months and three years in patients submitted to PCI with Taxus stents when compared to conventional stents [4].

Stent thrombosis and symptomatic graft occlusion

The thrombosis rate of Taxus stents at 12 months was

3.3%, surprisingly higher than that found in controlled randomized studies, where the rate of thrombosis of paclitaxel-eluting stents over one year was 0.7% (by the protocol of the study) or 0.8% (definitive or probable by the definition of ARC - Academic Research Consortium) [5,6]. The use of Taxus stents for long lesions and the number of implanted stents contributed to the increased rate of long-term thrombosis and complications (mean total length of implanted stents = 86.1 ± 47.9 mm; 33.2% of patients had total length of implanted stents greater than 100 mm).

On the other hand, the occlusion rate of symptomatic grafts in the SYNTAX trial was 3.4% over 12 months. This number is lower than that classically reported of 10% of occlusion of venous grafts over one year [7]. A better surgery technique allied to the intensive use of statins and antiplatelet agents may be responsible for the difference in these results.

The prognosis of these complications is also different. In drug-eluting stent thrombosis, the mortality rate varies between 30% and 45% and the occurrence of myocardial infarction is greater than 80% [5,8].

Cost-effectiveness

The results of the cost-effectiveness of the SYNTAX trial are awaited. To achieve complete revascularization, in the PCI Group there was a necessity of the implantation of 4.6 Taxus stents per patient. With a unit value for the Taxus stent in Brazil being around R$10,000.00 (about US $23,500.00), the cost, just for the devices is R$46,000.00 (about US $108,300.00). The additional cost of the greater necessity of further procedures and the continuous use of clopidogrel must also be taken into account.

Strokes

The rate of strokes over 12 months was 2.2% in CABG and 0.6% in the PCI Group. For the first time, an important study comparing surgery with angioplasty has reported this difference. The most obvious explanation is found in the design of the SYNTAX trial, which includes a population of more severe patients than those selected for controlled randomized studies, which generally exclude patients with more serious comorbidities.

The incidence of strokes after CABG is mainly related to the age of the patient and the presence of atherosclerotic plaque in the ascending and transverse aorta. Peri-operative atheroembolism from the aorta is responsible for at least one third of the cases of strokes after CABG due to the handling of the ascending aorta or aortic arch during cannulation, aortic clamping, preparation of proximal anastomoses or of the arterial cannula flow. Recent more rigorous methods to detect advanced atherosclerosis of the ascending aorta, as well as surgical strategies, such as the no-touch technique of off-pump surgery, may reduce the mobilization of aortic atheroma and prevent the occurrence of this event [9]. This finding reinforces the fact that surgery in this group of more seriously ill patients may evolve and improve the results.

Necessity of further revascularization

It has been demonstrated that drug-eluting stents are capable of reducing restenosis and the necessity of additional revascularization compared with the conventional stent, based on the data of controlled randomized studies. Nevertheless, when extrapolated to large national registers, with groups of patients from the real world, the difference is marginal. In the SCAAR trial, with a population more similar to the one of this study, the absolute reduction in restenosis rates between drug-eluting and conventional stents was 3% and of re-interventions of 1%, thus lower than rates in controlled randomized studies [4].

Anginal target

While CABG is effective in reducing angina, there are no data about the efficacy of drug-eluting stents compared to conventional stents in respect to angina. The comparative data at one and five years of follow up will be awaited.

Subgroups

In the analysis of patients with trunk lesions, the total MACCE at 12 months was lower with CABG (13.7% versus 15.8%). When stratified by diabetes, diabetic patients had a lower MACCE at 12 months after CABG than after PCI-Taxus (14.2% versus 26.0%).

Details of the operative technique

The mean number of grafts per patient was 2.8 and the mean number of distal anastomoses per patient was 3.2. Off-pump CABG was utilized in 15% of the patients, reflecting the reality in most North American and European centers that participated in the trial. Bilateral internal thoracic artery grafts were utilized in 27.6% of patients and complete arterial revascularization in 18.9%. However, it is interesting to note that an arterial graft was used for the anterior descending artery in 95.6% of the patients, not 100%, which should be the target in surgery. Complete revascularization was performed in 63% of the patients submitted to CABG against 57% in PCI.

SYNTAX register

Concomitantly, the results of the SYNTAX register were presented; 1275 patients of a cohort of 3075 patients initially selected (41.1% of the patients) and that were considered eligible for only one type of procedure. Thus, 1077 patients were allocated to the Surgical Group and 198 to the PCI Group.

This allocation was based on the clinical and anatomical characteristics: patients who were not candidates for CABG

(inoperative patients, n = 198) and patients who were not candidates for PCI (technically impossible, n = 1077). The main causes for ineligibility for CABG were severe morbidities (70.7%), lack of grafts (9.1%) and coronary arteries with bad quality distal beds (1.5%). In the PCI Group, the main causes were complex coronary anatomy (70.9%), chronic total occlusion of the coronary artery (22%) and impossibility of antiplatelet therapy (0.9%).

In the results, the death rates by any cause were 2.5% in CABG against 7.3% in PCI; myocardial infarction (2.5% CABG vs. 4.2% PCI); stroke (2.2% CABG vs. 0% PCI); compound death; stroke and myocardial infarction (6.6% vs. 10.5% PCI); new revascularization (3.0% CABG vs. 12% PCI); total MACCE (8.8% CABG vs. 20.4% PCI).

The final analysis of the register expresses the conclusion that CABG continues to be the only option for the treatment of at least 1/3 of patients enrolled with results that are considered excellent. Surgery presents the additional advantage of avoiding double antiplatelet therapy indefinitely and the associated risk of bleeding.

SYNTAX score

In this prospective study, the SYNTAX score was developed with the aim of stratifying patients for the best procedure. The SYNTAX score is based on the coronary anatomy in respect to the number of lesions and their functional repercussions, location and complexity. Higher SYNTAX scores are indicative of more complex conditions and potentially worse prognoses.

Thus the application of the SYNTAX score demonstrated that medium- and high-risk patients benefit from surgical treatment. The patients with lower risk had similar benefits from both procedures. This is indicative that lower-risk patients fit into the characteristics of patients from the MASS-2 and COURAGE studies and require additional evaluation to determine the benefit of the procedures.

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