SYNTAX mistakes

Los errores del estudio SYNTAX

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Abstract

This revision critically examines results from the SYNTAX study that was recently published the final follow up to 5 years. Therein patients with three-vessel coronary disease or left main trunk of coronary artery were randomized to be treated by coronary angioplasty with 1st generation of drug eluting stents versus coronary artery bypass surgery. In this manuscript we describe potential errors of that study such as: methodological mistakes, selection bias of patients, procedure and so as the technique employed to treat them. All these inaccuracies couldexplained the favorable results of bypass in some subgroups of this study.Maybethe number of stents per patients used and the design of them are the two major limitations of this trial making unable to apply it to the practice of angioplasty at the present time.

Key words: *SYNTAX trial, drug eluting stents, coronary artery bypass surgery, coronary artery disease.*

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INTRODUCTION

The SYNnergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) trial compared percutaneous coronary intervention (PCI) with coronary artery bypass graft surgery (CABG) in patients with unprotected left main (ULMD) disease or 3-vessel disease or both. The study was a non-inferiority trial and the primary end point of the study (major adverse cardiac and cerebrovascular events at 1 year [MACCE]) was not met because of the higher rate of repeat revascularization in the PCI arm. Secondary end points included MACCE at 5 years, rates of the individual component of MACCE, and rates of stent thrombosis or graft occlusion.[1,2]

MISTAKE # 1
An all comers study?

In the intention of the investigators, the SYNTAX trial was designed with broad inclusion criteria in order to enroll "all comer" patients with ULMD and/or 3 vessel-disease. Out of 4,337 screened patients, 1,262 (29%) were not included in the study and the large majority of these patients had a treatment preference or declined to participate. The Syntax investigators did not provide clinical details of this subset of patients (risk profile, need for urgent or emergency revascularization) that account for 30% of the screened cohort of patients. Another point with the potential for bias is that the number of patients that withdrawn consent after randomization was much higher in the CABG group (40 out of 897 patients) than in the PCI group (7 out of 903 patients). Finally a selection bias was introduced with the PCI and the CABG registries: 1275 eligible for the study were not randomized and included in the CABG registry (1,077 patients) or in the PCI registry (198 patients). The 2 main reasons for the inclusion in the CABG registry was the presence of chronic total occlusion that was considered nonsuitable for PCI treatment by the local interventional cardiologist and a low EuroSCORE (3.9±2.7), while the main reason for the inclusion in the PCI registry was a high EuroSCORE (5.8±3.1 in the Registry and 3.8±2.6 in randomized PCI arm). Finally, only 41% of patients from the initial cohort of 4,337 patients were randomized to PCI or CABG (1,800 patients).[1] For these reasons the SINTAX trial cannot be considered as an all comers study.

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Conflictos de intereses: no existen.

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MISTAKE # 2
The impact of the selection process on the characteristics of the randomized population and on the main results of the study

The used selection process resulted in the randomization of a low surgical risk population: Euroscore 3.8±2.6 of the PCI arm and 3.8±2.7 of the CABG arm.[1] Thus the study compared PCI with CABG in a low surgical risk population and with a low predicted mortality in patients treated with CABG, it is difficult or even impossible to show the potential benefit of PCI in terms of mortality.

MISTAKE # 3
The primary end point

The primary clinical end point was a composite of major adverse cardiac and cerebrovascular events (i.e., death from any cause, stroke, myocardial infarction, or repeat revascularization) throughout the 12-month period after randomization. The primary end point rate was 12.4% in the CABG arm and 17.8% in the PCI arm (p=0.002). The difference between group was driven by the higher rate of revascularization in the PCI arm (13.5% vs 5.9%, p < 0.001), while, as expected, there were no difference between arms in the rate of death and myocardial infarction. The rate of stroke was higher in the CABG arm (2.2% vs 0.6%, p=0.003).[1] Beyond the intrinsic limitations of all composite end points that consider as equivalent clinical event s with very different weights (death = stroke = repeat revascularization), it should be outlined that other adverse events related to surgery were not considered such as sternum wound, sternum reopened, reintervention for bleeding, need for blood transfusion.

MISTAKE # 4
The heterogeneity of performance of the participating centers

Unpublished data show an extreme variability in the performance of the centers involved in the study: among the 85 sites, the incidence of the primary end point ranged from 0 to more 40% in patients randomized to CABG (11 centers without MACCE; 1 top enroller center with >40% of MACCE) or PCI (3 centers without MACCE; 1 center with >50% of MACCE (. Only 1 top enroller center had 0 MACCE with surgery or PCI. This variability could be considered as a "real world" clinical practice, but a clinical study comparing 2 treatments should focus on the "real world patients" and exclude centers with an unacceptable high rate of adverse events and very far from a standard or excellent performance.

MISTAKE # 5
The (in)completeness of revascularization

Patients were treated with the intention of achieving complete revascularization of all vessels at least 1.5 mm in diameter with stenosis of ≥ 50%.[1] This goal was achieved in a number of patients lower than expected in both randomized arms (56.7% in the PCI arm, and 63.2% in the CABG arm, p=0.005). The high rate of incompleteness of revascularization had no impact in the randomized surgical cohort: at 3 years there were no significant differences in outcome of patients randomized to surgery and with or without complete revascularization.[3] Conversely, more recently, the same investigators could demonstrate in "all comers" (randomized and nested registry: PCI n=1,095, CABG n=1,541) patient cohort a strong detrimental effect on outcome of the incompleteness of revascularization both in the PCI arm and the CABG arm.[4] At 4-year follow-up, the MACCE rate and mortality rate were higher in patients with incomplete revascularization: in PCI arm MACCE rate was 41.9% in patients with incomplete revascularization and 29.6% in patients with complete revascularization (p<0.001); in the CABG arm MACCE rate was 26.2% with incomplete revascularization and 20.6% with complete revascularization (p=0.013). In the PCI arm the 4-year cardiac mortality was 9.1% and 6.0% in patients with incomplete or incomplete revascularization, respectively (p=0.049), and in the CABG arm 5.6% and 2.9%, respectively (p=0.01). Other notable findings of this post-hoc analysis are that coronary chronic total occlusion (CTO) is predictive of incomplete revascularization, and that incompleteness of revascularization can be considered as a marker of higher anatomical and clinical complexity according to the SYNTAX score and EuroSCORE of patients who were incompletely revascularized. In this post-hoc analysis CTO is frequent in patients with ULMD and 3-vessel disease (1,007 CTO in 2,636 patients), but the rate of CTO PCI success was very low (49.4%) as well as the rate of performed CTO graft.[4]

MISTAKE # 6
Subgroup analyses

Since the primary end point of the study was not met (non-inferiority of PCI as compared to CABG in MACCE at 1 year follow-up) subgroup analyses should not be allowed. However, starting from the main paper published in 2009, the SYNTAX investigators performed several subgroup analyses stating in advance that specific information for each subgroup is of an observational nature and only hypothesis generating. Despite this concern, the results of these inappropriate analyses had a significant impact on the European and American guidelines and CABG is still con-

sidered the gold standard for coronary revascularization in patients with ULMD and or 3-vessel disease.[5,6].

MISTAKE # 7

The dissociation between anatomic complexity and clinical complexity

In "real world" patients frequently anatomic complexity parallels clinical complexity. In centers with routine PCI for ULMD and or 3 -vessel disease the clinical profile is very similar to the one of SYNTAX PCI registry: many patients are admitted for an acute coronary syndrome, are elderly, have left ventricular dysfunction and need urgent revascularization.[7,8] One third of these patients has at least 1 CTO, and in the large majority of cases the left main lesion involves a bifurcation or a trifurcation. Again, in the SYNTAX trial it has been shown that incomplete revascularizationafter PCI or CABG is associatedwith high degree anatomical complexity, and in the same study the best way to predict outcome after revascularization is to score the risk including clinical and anatomical variables.[4,9] Thus, it is very difficult to accept a cut off of SYNTAX score for the more appropriate revascularization strategy (PCI or CABG) in the "real world" patient.

MISTAKE # 8

Disparity in follow-up rate between the randomized arms

The 5-year outcome was a secondary end point of the study. At 5 years, MACCE rate was higher in the PCI arm as compared to CABG (37.3% and 26.9%, respectively, p<0.0001).[2] The difference between arms was driven by the higher rate of repeat revascularization and myocardial infarction in the PCI arm. Conversely, there were no difference between groups in mortality (11.4% in CABG arm and 13.9% in the PCI arm; p=0.10) while with regard to stroke there was a trend favoring PCI (3.7% in CABG arm and 2.4% in the PCI arm; p=0.09). A major concern in the long-term follow up is the disparity in follow-up rate between groups: originally, 897 patients were randomized to CABG and 903 to PCI; after 1 year 849 patients randomized to CABG remained in the study (40 patients withdrew consent and 8 were lost) while 891 randomized to PCI remained in the study (7 withdrew consent, and 5 were lost); at 5 years, 805 CABG patients remained in the study (10 withdrew consent, and 34 were lost) while 871 PCI patients remained in the study (4 withdrew consent and 16 were lost). Thus, 92 patients out of 897 randomized to CABG withdrew consent or were lost, while only 55 patients randomized to PCI withdrew consent or were lost. In order to overcome the disparity in the percentage of non-assessable patients between groups the SYNTAX investigators performed a sensitivity analysis that showed higher MACCE rate in the PCI arm irrespective of whether all lost patients were considered to be dead or alive and event free. However, the sensitivity analysis shows that if all non-evaluable patient are thought as having dead, the 5-year mortality rate is lower in the PCI arm than the CABG arm: 17.2% and 21.1% respectively; RR=0.81 (0.67-0.99); p=0.04.[2]

MISTAKE # 9

Obsolescence of the TAXUS stent

In the randomized PCI arm more than four stents on average were implanted per patient, and a third of patients had placement of stents with a total length of more than 10 cm.[1] Considering the high percentage of incomplete revascularization (43.3%) and the total stent length, the performance of the TAXUS stent in terms of safety was relatively good: the stent thrombosis rate at 1 year was 3.3%. Conversely, the performance in terms of efficacy was lower than expected considering the high percentage of patients that needed a repeat revascularization (14.2%). The stent performance can be considered largely out-of-date, when considering the results of randomized trials comparing new generation stents with TAXUS, and of registries in clinical settings at high risk of restenosis and thrombosis such as ULMD and long CTO.[10-14] It" very likely that the SYNTAX trial would have been a positive study if a second generation drug eluting had been used instead of first generation paclitaxel-eluting stent.[14,15]

WHAT HAVE WE LEARNT FROM THE SYNTAX TRIAL?

First, it seems impossible to perform a true all comers study, and it has been shown that using broad inclusion criteria the risk profile of patients excluded from randomization remains worse as compared to randomized patients.[16] Second, for patients with low surgical risk the 2 revascularization strategies provide similar long-term survivals. Third, it is unknown if PCI is superior to CABG in high risk patients with ULMD or 3-vessel disease, and future studies should focus on these patients for the definition of the best revascularization technique in these patients. Fourth, whatever the revascularization technique used, the goal of complete revascularization should be considered in all patients.[17-19]

RESUMEN

Se analizan críticamente los resultados del seguimiento final a 5 años del estudio SYNTAX, que fueron recientemente publicados. En el estudio se asignaron aleatoriamente pacientes con enfermedad de tres vasos coronarios y/o tronco de coronaria izquierda a tra-

tamiento por angioplastia coronaria con *stent* farmacológico de 1ra generación *versus* cirugía de bypass coronario.

El autor en esta revisión describe los errores del estudios como: metodológicos, de selección de pacientes, de procedimiento, así como de la técnica utilizada. Todos ellos pueden explicar los resultados favorables a la cirugía de revascularización en alguno de los subgrupos de este estudio. Probablemente el número de *stents* utilizados y el diseño del mismo sean las dos mayores limitantes de este *trial* para aplicarlo a la práctica de angioplastia en el momento actual.

Palabras clave: *estudio SYNTAX, stents liberadores de fármacos, cirugía de bypass coronario, enfermedad coronaria.*

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