

Lessons from the clinical trials FREEDOM and SYNTAX 5-years: new evidence or evidence only noticed now?

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“There are many hypotheses in science which are wrong. That’s perfectly all right: it’s the aperture to finding out what’s right”

Carl Sagan

“There is nothing new under the sun - nihil novi sub sole”

Ecclesiastes 1:9

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In recent weeks, the two most important and awaited scientific evidence in the treatment of multivessel coronary disease after eluting stents were released: the results from the FREEDOM study [1] and the 5-year analysis of the SYNTAX trial [2]. In a current scenario, in which the roles of intervention, surgery and medical treatment are increasingly discussed, and in which it is increasingly spread the need for therapeutic decision by multidisciplinary heart teams, the critical analysis of methodologically well-designed studies that bring a broader clinical applicability than previously published trials comparing angioplasty and coronary artery bypass surgery, becomes widely needed.

However, if the main findings of both studies are not surprising, reasserting the role of revascularization surgery as preferred in patients with multivessel disease, a more detailed assessment of the body of evidence previously available will show that the information is already in the literature.

The final analysis of 5-year follow-up of the SYNTAX trial, presented at the European Congress of Cardiothoracic Surgery in October, confirmed the strategy of revascularization, as more beneficial than the implantation of drug-eluting stents for patients with lesions of left main

coronary artery or multivessel coronary heart disease and additionally separation was observed in the curves of some outcomes in relation to the previously published analyzes of 1 to 3 years of follow up. The rates of cardiovascular death and myocardial infarction, which previously did not reach statistical significance, were significantly higher in the PCI group (9.2% vs. 4.0% and 10.6% vs. 3.3%, respectively - $P < 0.001$). Moreover, the rate of cerebral vascular accident (CVA), higher in the surgical previous analyzes, proved to be similar between groups after 5 years (3.0% vs. 3.4% - $P = 0.66$).

Before this evidence, in April of this year, the record ASCERT [3] already signaled with similar results. Evaluating a robust sample of nearly 200,000 patients who underwent CABG ($n = 86.244$) or angioplasty with stents ($n = 103.549$), a study funded by the National Heart, Lung, and Blood Institute revealed on 4 years of follow up, mortality 20% lower in operated cases compared to cases intervened by catheter (16.4% vs. 20.8%, CR 0.79 - 95% CI 0.76 to 0.82 - $P = 0.002$), which was effective similar evaluation of other variables, and in comparison between subgroups.

Even more remotely, this information was already available in the publication of results from the registry of the Department of Health of the State of New York [4]. Evaluating all cases of coronary artery bypass grafting ($n = 7437$) and implantation of pharmacological stents ($n = 9963$) conducted in that state between 2003 and 2005,

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Abbreviations, acronyms and symbols	
ASCERT	American College of Cardiology Foundation-The Society of Thoracic Surgeons collaboration on the Comparative Effectiveness of revascularization sTrategies
CVA	Cerebrovascular accident
BARI	Bypass Angioplasty Revascularization Investigation
EVASTENT	EVALuation of active STENT
EXCEL	Evaluation of XIENCE PRIME™ Everolimus Eluting Stent System (EECS) or XIENCE V® EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
FREEDOM	Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal Management of multivessel disease
MACCE	major adverse cardiovascular and cerebrovascular event
SYNTAX	SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery

this portrait of the real world revealed differences in the outcomes of interest, in 18 months of follow-up hitherto not revealed by clinical trials. In patients with lesions in three or more vessels, the survival rate favored the surgical group (94% vs. 92% - $P = 0.03$), and the rate of survival free of myocardial infarction (92% vs. 89% - $P < 0.001$). Also, in the group with lesions in two vessels, the same analysis of outcomes showed benefit with revascularization strategy (96% vs. 94% - $P = 0.003$ and 94.5% vs. 92.5% - $P < 0.001$). And, as expected, the rate of subsequent revascularization was much higher in the group undergoing angioplasty.

Another alleged "gap" of evidence in the treatment of coronary artery disease concerned what type of intervention should be preferred in patients with multivessel disease with diabetes mellitus.

In the FREEDOM trial, coronary surgery was compared to angioplasty with drug-eluting stents, in 1,900 diabetic patients with multivessel disease were randomized into 140 different institutions, in which all patients received optimal therapy to control cholesterol, blood pressure and glycosylated hemoglobin. The primary endpoint was previously defined as death from any cause, non-fatal myocardial infarction and / or stroke, and occurred more frequently in the PCI group (27% vs. 19%, $P = 0.005$), after 5 years of follow up. A more detailed analysis of outcomes so-called "hard" also demonstrated the benefit of surgery on the lower occurrence of myocardial infarction ($P < 0.001$) or death from any cause ($P = 0.049$). On the other hand, stroke was the most frequent in the surgery group (5.2% vs. 2.4%, $P = 0.03$). The authors concluded that "in diabetic patients with advanced coronary disease, bypass surgery is superior to angioplasty, by significantly

reducing the rates of death and myocardial infarction, although with higher rates of stroke."

In fact, in the subgroup of diabetic patients, information that CABG offers more benefit than PCI, and that, in particular, among the types of stents, those coated with drugs have worse outcomes in this population, was already included in the results of some other important studies.

In the final analysis of the BARI study [5], which compared the performance of surgical and percutaneous revascularization in multivessel coronary disease, there was no difference in late survival when evaluated the total sample ($n = 1,829$). However, following 5 and 10 years of diabetic subgroup ($n = 353$), there was a lower mortality from all causes, lower cardiovascular mortality and lower rate of myocardial infarction in patients who underwent CABG, and not the percutaneous angioplasty ($P = 0.002$).

Moreover, in the French multicenter registry EVASTENT [6], 1,731 patients with multivessel coronary artery disease, revascularization exclusively with sirolimus stents had their outcomes measured in the 1 year follow-up, although overall survival free of major cardiovascular events (MACCE) has been excellent (98%), assessment of diabetic patients showed mixed results. While at one extreme 99% of non-diabetic patients with univascular disease were free of MACCE, amongst diabetic patients with multivessel disease only 87% showed no severe outcomes at 1 year. And an even more important finding: when analyzed only all-cause mortality, independent of the patient be uni, bi, or multiarterial, the condition of being diabetic increased by 3.1 times the chance of death - $P < 0.001$ (Figure 1).

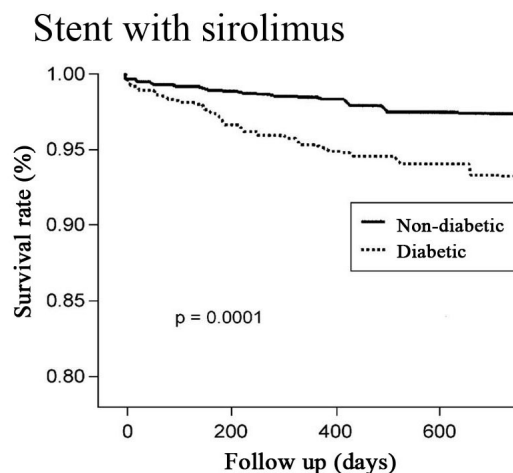


Fig. 1 – EVASTENT study [6]: late survival in diabetic and non-diabetic patients after stenting with sirolimus

Another important revelation, but not surprising, arises when evaluated outcomes so-called "hard" of implantation of bare-metal stents versus drug-eluting stents, as in the combined analysis of four randomized trials in patients with multivessel disease [7]. In the population of 428 diabetic patients, the survival rate at 4 years was significantly lower in those who received sirolimus-eluting stents (87.8%) compared to bare-metal stents (95.6%). In other words, the condition of the pharmacological stent be increased by 2.9 to an odds ratio of death from any cause, in diabetic patients, due to the higher incidence of late thrombosis (95% CI: 1.38 to 6.10 - Figure 2).

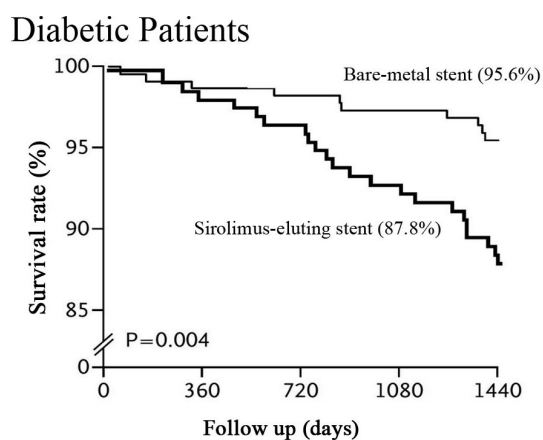


Fig. 2 - Analysis of long-term survival of diabetic patients after implantation of sirolimus-eluting stents or bare-metal stents [7]

Finally, while the results are awaited for further studies in progress, as the EXCEL trial [8], which evaluates the performance of the everolimus eluting stent vs. revascularization surgery in patients with lesions of left main coronary artery, a careful reading of the body of evidence available for some time in the literature may reveal "truths" that seemingly emerge only now, in the light of the findings of large multicenter clinical trials.

As the millennial initial quote "There is nothing new under the sun - nihil novi sub sole", most "new" evidence in the treatment of ischemic heart disease, in particular

those relating to the controversy vs. angioplasty, is not exactly new, and always within reach of our eyes; it was only a matter of willingness to see them.

REFERENCES

1. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, et al. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med*. 2012. DOI: 10.1056/NEJMoa1211585.
2. Taggart D. Surgery is best for most patients, final SYNTAX data confirm. Disponível em: <http://www.theheart.org/article/1466345.do>.
3. Weintraub WS, Grau-Sepulveda MV, Weiss JM, O'Brien SM, Peterson ED, Kolm P, et al. The ASCERT Study Investigators. Comparative effectiveness of revascularization strategies. *N Engl J Med*. 2012;366(16):1467-76.
4. Hannan EL, Wu C, Walford G, Culliford AT, Gold JP, Smith CR, et al. The Registry of New York State Department of Health. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med*. 2008;358(4):331-41.
5. BARI Investigators. The final 10-year follow-up results from the BARI randomized trial. *J Am Coll Cardiol*. 2007;49(15):1600-6.
6. Machecourt J, Danchin N, Lablanche JM, Fauvel JM, Bonnet JL, Marliere S et al. Risk factors for stent thrombosis after implantation of sirolimus-eluting stents in diabetic and nondiabetic patients: the EVASTENT Matched-Cohort Registry. *J Am Coll Cardiol*. 2007;50(6):501-8.
7. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med*. 2007;356(10):989-97.
8. The EXCEL Trial Investigators. Evaluation of Xience Prime™ Everolimus Eluting Stent System (EECSS) or Xience V® EECSS versus coronary artery bypass surgery for effectiveness of left main revascularization. Disponível em: <http://www.clinicaltrials.gov/ct2/show/NCT01205776>.