

Complete revascularization and diabetes in the real world: observational data as a necessary addition to clinical trials



Revascularización completa y diabetes en el mundo real: datos observacionales como complemento necesario de los ensayos clínicos

Alejandro Travieso and Pablo Salinas*

Servicio de Cardiología, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain

SEE RELATED CONTENT:

<https://doi.org/10.24875/RECICE.M22000308>

Diabetes mellitus is a comorbidity that is present in 20% to 30% of the patients with coronary artery disease and an indication for revascularization. Also, it poses a scenario of greater complexity for several reasons. The presence of diabetes is associated with more extensive, diffuse, calcified coronary artery disease, and graft and stent failure. All of it is associated with a higher risk of repeat revascularizations and worse prognosis for the patients, which is why diabetes is a differential element here since it establishes the revascularization method in patients with multivessel disease based on the clinical practice guidelines.¹ Currently, the recommendation of coronary artery bypass graft (CABG) is superior to percutaneous coronary intervention (PCI) in diabetic patients. This indication comes from numerous studies being the FREEDOM trial² one of the most important of all. However, are patients from the routine clinical practice or real-world patients similar to those included in these clinical trials?

In this sense, the study conducted by Puyol-Ruiz et al.³ recently published in *REC: Interventional Cardiology* provides valuable observational information on the results of coronary revascularization in diabetic patients in the routine clinical practice. This study shows the results from a historical cohort (2012-2014) of 733 patients with diabetes and multivessel coronary artery disease with a clinical indication for coronary angiography. Authors divide the study population based on the degree of revascularization (complete or incomplete) and the clinical profile consistent, or not, with the inclusion criteria of the FREEDOM clinical trial.² In this cohort, 80.8% and 14.5% of the patients were revascularized percutaneously and surgically, respectively compared to 4.8% who received medical therapy only. Authors found a tendency towards a lower rate of clinical events at 35-month follow-up in patients with complete revascularization. Also, both the risk profile and the rate of events of the FREEDOM study population (41%) was significantly lower compared to the non-FREEDOM study population (59%): lower rate of death (5.5% vs 38.4%; $P = .006$), cardiac death (3.2% vs 31.2%; $P = .002$), and major adverse cardiovascular events (6.5% vs 40.0%; $P = .012$). Therefore, we can deduce that patients from the FREEDOM trial are a selected subpopulation of lower risk representative of less than half of the real-world patients with

diabetes and multivessel disease. Other studies that have tried to identify, in a population from the real-world clinical practice, the group of patients potentially eligible for clinical trial show similar prevalences (around 50%) of selection criteria for clinical trials on coronary revascularization, a population that also shows a significantly lower rate of cardiovascular adverse events.⁴

On the other hand, regarding the interpretation of these data, we should remember that over 10 years have passed since the FREEDOM trial, and the recruitment phase into the cohort of the study conducted by Puyol-Ruiz et al.³ Let's see what elements have changed in the revascularization of diabetic patients through all this time.

Modern PCI is not similar to the one described in the FREEDOM trial that used first-generation drug-eluting stents (sirolimus in 51%, and paclitaxel in 43%). Current platforms have exceeded paclitaxel-eluting stents in multiple clinical settings including diabetic patients.⁵ Sirolimus-eluting stents had higher rates of thrombosis and stent failure compared to current stents in relation to the mechanisms of hypersensitivity to polymer.⁶ Also, ultrathin strut drug-eluting stents have proven to be associated with a lower rate of adverse events compared to first-generation stents ($> 120 \mu\text{m}$).⁷ As a matter of fact, more recent studies with all-comers design have demonstrated that state-of-the-art stents like the polymer-free amphillimus-eluting stent improves results even more (target lesion failure) compared to second-generation reference stents.⁸ This huge improvement in stent technology seen over the last few years, the calcified plaque modification techniques used, and the intracoronary imaging modality-guided PCI performed or with pressure guidewires lead us to think that the current PCI results improve significantly those reported both in the FREEDOM trial and in this cohort of patients. Such statement can be confirmed in the comparison between the SYNTAX II cohort and the SYNTAX PCI group that used paclitaxel-eluting stents.^{9,10}

However, CABG results have also improved, at least, in the clinical trials. For example, the 1-year rate of adverse events (death, myocardial infarction, stroke or repeat revascularization) has dropped from 12.4% in the CABG group of the SYNTAX trial¹⁰ down to 6.9% in the CABG group of the FAME 3 trial.¹¹ This reduction is probably

* Corresponding author.

E-mail address: salinas.pablo@gmail.com (P. Salinas).

[@pablosalinas](#)

Online: 02-09-2022.

2604-7322 / © 2022 Sociedad Española de Cardiología. Published by Permanyer Publications. This is an open access journal under the CC BY-NC-ND 4.0 license.

due to better perioperative care and the optimal medical therapy since no major changes in the surgical technique have been reported.

Regarding the impact diabetes has on the results of complete revascularization, the results from the study conducted by Puyol-Ruiz et al.³ are consistent with a meta-analysis of 28 studies and 83 695 patients published by Zimarino et al. This analysis revealed that complete revascularization produced similar benefits in diabetic and non-diabetic patients in terms of mortality and adverse events reporting, in the former, significantly lower rates of new myocardial infarctions.¹² Despite this benefit, the numbers of residual coronary artery disease are still high both in the present study (CABG 49/106 [46.2%], PCI 396/592 [66.9%]), and in other PCI cohort studies (28.6%)¹³ or CABG (33.1% with residual SYNTAX score > 18.5¹⁴). Therefore, there is this doubt on whether incomplete revascularization is just a technical problem or else a risk marker associated with a more advanced stage of the disease.

In conclusion, the therapeutic management of multivessel coronary artery disease in diabetic patients is still challenging for cardiology today. While clinical trials keep being conducted in selected low-risk populations it'll be of paramount importance to complement them with information from the results of the actual clinical practice as this article did. In future studies we should make all the necessary efforts to use pragmatic designs where exclusion criteria are minimized to encourage their immediate applicability to the routine clinical practice.

FUNDING

None whatsoever.

AUTHORS' CONTRIBUTIONS

P. Salinas designed, supervised, reviewed, and drafted the manuscript. A. Travieso drafted and reviewed the original manuscript version.

CONFLICTS OF INTEREST

None reported.

REFERENCES

1. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87-165.
2. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for Multivessel Revascularization in Patients with Diabetes. *N Engl J Med.* 2012;367:2375-2384.
3. Puyol-Ruiz F, Chueca-González EM, Carrasco-Chinchilla F, et al. Clinical impact of complete revascularization on real-life diabetic patients. *REC Interv Cardiol.* 2022;4:343-350.
4. Hordijk-Trion M, Lenzen M, Wijns W, et al. Patients enrolled in coronary intervention trials are not representative of patients in clinical practice: Results from the Euro Heart Survey on Coronary Revascularization. *Eur Heart J.* 2006;27:671-678.
5. Kaul U, Bangalore S, Seth A, et al. Paclitaxel-Eluting versus Everolimus-Eluting Coronary Stents in Diabetes. *N Engl J Med.* 2015;373:1709-1719.
6. Virmani R, Guagliumi G, Farb A, et al. Localized Hypersensitivity and Late Coronary Thrombosis Secondary to a Sirolimus-Eluting Stent: Should We Be Cautious? *Circulation.* 2004;109:701-705.
7. Madhavan MV, Howard JP, Naqvi A, et al. Long-term follow-up after ultrathin vs. conventional 2nd-generation drug-eluting stents: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J.* 2021;42:2643-2654.
8. Romaguera R, Salinas P, Gomez-Lara J, et al. Amphillimus- vs. zotarolimus-eluting stents in patients with diabetes mellitus and coronary artery disease: the SUGAR trial. *Eur Heart J.* 2022;43:1320-1330.
9. Banning AP, Serruys P, De Maria GL, et al. Five-year outcomes after state-of-the-art percutaneous coronary revascularization in patients with de novo three-vessel disease: final results of the SYNTAX II study. *Eur Heart J.* 2022;43:1307-1316.
10. Serruys PW, Morice M-C, Kappetein AP, et al. Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease. *N Engl J Med.* 2009;360:961-972.
11. Fearon WF, Zimmermann FM, De Bruyne B, et al. Fractional Flow Reserve-Guided PCI as Compared with Coronary Bypass Surgery. *N Engl J Med.* 2022;386:128-137.
12. Zimarino M, Ricci F, Romanello M, Di Nicola M, Corazzini A, De Caterina R. Complete myocardial revascularization confers a larger clinical benefit when performed with state-of-the-art techniques in high-risk patients with multivessel coronary artery disease: A meta-analysis of randomized and observational studies. *Catheter Cardiovasc Interv.* 2016;87:3-12.
13. Park TK, Hahn JY, Yang JH, et al. Modified residual SYNTAX score and clinical outcomes in patients with multivessel disease undergoing percutaneous coronary intervention. *EuroIntervention.* 2017;13:87-96.
14. Melina G, Angeloni E, Refice S, et al. Clinical SYNTAX score predicts outcomes of patients undergoing coronary artery bypass grafting. *Am Heart J.* 2017;188:118-126.