

A sweet decision: treatment of stable coronary artery disease in patients with diabetes mellitus

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The numbers of patients with coronary artery disease (CAD) are increasing globally and stable CAD with its symptoms of angina pectoris and increased risk of coronary events despite decreasing mortality is a serious health problem (1). Especially patients with diabetes mellitus are at high risk for development of CAD as well as subsequent coronary events associated with high mortality (2). Indeed, the extent of CAD seems to be increasing faster in patients with diabetes mellitus compared to patients without it independent of other classical risk factors. Therefore, patients with CAD and diabetes mellitus are at exceptional risk and are thought to need best medical as well as revascularization treatment (3). Nevertheless, little data is available whether treatment decisions need to be tailored to the individual extent of CAD in patients with diabetes mellitus or whether patients need to be treated similar irrespectively of their CAD status.

What are the available options for those patients today?

The first question (1) is whether the patient needs revascularization on top of medical therapy or whether medical therapy alone might be best suited to treat CAD in the individual patient. The follow-up discussion (2) includes the question whether percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is the optimal choice for the individual at risk, when the treatment

goal is revascularization (3). Whether the extent of CAD influences these decisions is rather understudied.

The first question is the main question of the BARI-2D trial published in 2009 (4). That trial showed superiority of CABG versus medical therapy, which was not shown for the PCI group versus medical therapy in this study. Nevertheless, a comparison between CABG and PCI patients was difficult to do, since the type of revascularization strategy was not randomized and made up before final inclusion into the trial. Therefore, patients were not comparable, especially when the extent of CAD was considered. Indeed, there were higher levels of CAD in patients in the CABG group. This might have favored the outcome in the CABG group, since revascularization seems to be more successful in high risk patients with greater extent of CAD (5).

The extent of CAD is difficult to access, but so far, the SYNTAX (synergy between percutaneous coronary intervention with TAXUS and cardiac surgery) score is one of the better tools to investigate this in a standardized fashion (6,7). Clearly, higher SYNTAX scores are known to be associated to worse outcomes. Nevertheless, it remains less clear whether a revascularization strategy can improve outcomes to a higher extent in high risk SYNTAX patients compared to low risk SYNTAX patients.

This is one of the questions addressed in the current paper by Ikeno and colleagues. The published manuscript (5) had the aim to show the predictive ability of the SYNTAX

score in terms of major cardiovascular events and to show that revascularization would have a greater effect compared to medical therapy in patients with a higher SYNTAX score and thus a more widespread CAD. To address this, Ikeno and colleagues utilized the BARI-2D data. Indeed, they show convincingly that higher SYNTAX scores are associated to worse outcome (5). This finding is less surprising and is in line with other studies suggesting a similar outcome. The other question addressed in this paper is the benefit of revascularization as well as the benefit of the different types of revascularization, namely CABG or PCI. Indeed, no benefit was shown in the hard endpoint death, myocardial infarction as well as stroke by any revascularization strategy, independent whether it is CABG or PCI in patients with a low Syntax score ≤ 22 (5). This is interesting and adds to the discussion whether medical therapy alone might be the optimal choice in lower risk individuals with stable symptoms and diabetes mellitus. At least no harm was reported in either group independent of the revascularization strategy.

The more interesting groups are the high-risk groups with a SYNTAX score >22 . Here, CABG could improve outcome significantly over the 5 year follow up compared to medical therapy. This was not shown in the PCI group. Importantly, there was even a strong trend to inferiority of the PCI group with numerically more endpoints reached after PCI compared to medical therapy alone (5).

This was the opposite of what was expected by the authors and probably most interventional cardiologists alike. Nevertheless, similar data come from the other large trial investigating revascularization in patients with stable CAD and diabetes mellitus, the FREEDOM trial (8). The FREEDOM trial published in 2012 demonstrated superiority of CABG versus PCI. Indeed, this was a randomized trial in view of both revascularization strategies. Based on the results of the BARI-2D and FREEDOM trial there is the recommendation for treatment with CABG using arterial grafts for revascularization by the guidelines of the European Association of Cardiology (9) in patients with stable CAD and diabetes mellitus.

In the background of the current recommendations there is need to strengthen the use of the SYNTAX score in decision making regarding myocardial revascularization. This will enable smarter decision making benefiting those patients. What does this study by Ikeno *et al.* (5) further add. Given that revascularization was only beneficial in patients with a SYNTAX score >22 , one would advise CABG only in those patients with severe CAD but not in

the ones with lower risk. This does not necessarily reflect current practice in many countries and this study should remind all physicians involved in decision-making of these results.

Further, which important message should be reminded of the rather negative results in the PCI group? FREEDOM and BARI 2-D used first generation drug eluting stents or bare metal stents (BARI 2-D) for PCI (4,8). This is indeed inferior to modern second generations stents, but mostly for repeated revascularization and less for hard endpoints, which are presented in the current study. Especially in patients with a SYNTAX score >22 many lesions needed balloon dilatation followed by stent implantation, which might have resulted in long segments being treated with devices with some drawbacks. Obviously, functional anatomy was not assessed in all stenosis e.g., by FFR, further aggravating the number and length of stents. The longer the stented area, the worse the outcome will be, which might explain the negative results presented here. Therefore, spot stenting leaving less footprint in the coronary circulation is essential in current PCI revascularization. Another caveat is that one needs to consider that only few patients in the PCI strata had a very high SYNTAX trial making the general results less strikingly. Therefore, the generalizability of the data is rather limited and future studies need to address this in more detail.

Considering this, current trials utilizing modern PCI strategies are shedding a more optimistic light on PCI in multi-vessel disease patients, at least in those without diabetes mellitus. Results of two major recent trials comparing CABG with PCI in complex CAD with left main disease using only second generation drug eluting stents for PCI and most often arterial coronary bypass grafting showed different results. The EXCEL (10) trials main message was that after a three-year period PCI of the left main is not inferior to CABG and that it can be applied in clinical use. On the contrary, the NOBLE (11) trial with a longer follow-up of 5 years showed the most benefit by CABG after a follow-up of 2 to 3 years, while the benefit resulted from repeated revascularization mostly with hard endpoints being also similar.

Thus, there is still debate which method should be preferred in complex CAD and especially in patients with comorbidities. In this context, it must be added that most decisions in stable disease are discussed in a local heart team, consisting of cardiovascular surgeons and interventional cardiologists meaning that the everyday clinical standard may differ from the recommended in the current guidelines.

However, as in all medical therapies, there should be ongoing research in terms of optimizing the results and to elucidate which is the best treatment at that current time as with ongoing time new techniques and treatment options are available which might perform better. In all still the way is the aim and there must be more research to answer the question to the optimal revascularization strategy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Moran AE, Forouzanfar MH, Roth GA, et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. *Circulation* 2014;129:1483-92.
2. Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 1999;100:1134-46.
3. Task Force M, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;34:2949-3003.
4. Group BDS, Frye RL, August P, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360:2503-15.
5. Ikeno F, Brooks MM, Nakagawa K, et al. SYNTAX Score and Long-Term Outcomes: The BARI-2D Trial. *J Am Coll Cardiol* 2017;69:395-403.
6. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 2009;5:50-6.
7. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961-72.
8. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;367:2375-84.
9. Authors/Task Force members, Windecker S, Kolh P, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;35:2541-619.
10. Stone GW, Sabik JF, Serruys PW, et al. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. *N Engl J Med* 2016;375:2223-35.
11. Mäkikallio T, Holm NR, Lindsay M, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet* 2016;388:2743-52.

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