The FREEDOM trial: a definitive answer to coronary artery bypass grafting or stents in patients with diabetes and multivessel coronary artery disease

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For the last two decades, there has been intense debate between cardiologists and surgeons regarding what the most effective mode is, of revascularization in patients with diabetes already receiving optimal medical therapy, who additionally require invasive coronary artery intervention on symptomatic and/or prognostic grounds. The debate began in earnest with the original interim analyses of the BARI trial, suggesting a survival advantage for the subset of patients with diabetes receiving coronary artery bypass grafting (CABG) rather than angioplasty [1], and was confirmed in the final 10-year follow-up with respective survival rates of 58 vs 46% (P = 0.025) [2]. Since then, the recent publications of the 5-year outcomes of the SYNTAX Trial [3] and the ASCERT registry [4] have provided strong evidence that CABG, in comparison with percutaneous coronary intervention (PCI), offers a strong survival benefit as well as a marked reduction in myocardial infarction (MI) and repeat revascularization in patients with intermediate and more severe coronary artery disease (CAD) as judged by SYNTAX scores of >22.

Because of the perception that patients with diabetes often have more severe and aggressive forms of CAD, intuitively there is an impression that they are also therefore likely to derive greater clinical benefit from CABG than from PCI. Others have argued, however, that significant advances in both medical therapy and stent technology would have eliminated the former—if any—benefit of CABG over PCI. Consequently, until the recent publication of the FREEDOM Trial [5], the relative merits of both interventions in patients with diabetes have also been fiercely debated. The main reason for the controversy was that, until the FREEDOM Trial, there was not a single trial in patients with diabetes, adequately powered, to give a definitive answer regarding whether CABG offered a survival or any other clinical benefit over PCI. It is therefore informative not only to examine the results of the FREEDOM trial, but also in the context of whether its findings are consistent with other evidence.

The FREEDOM trial randomized 1900 patients with diabetes and multivessel CAD, already receiving aggressive medical therapy, to CABG or PCI with drug-eluting stents. This trial therefore included more patients with diabetes than the total from all the subgroups from the other randomized trials. The primary 5-year composite outcome of death from any cause, non-fatal MI or stroke, occurred in 26.6% of the PCI group and 18.7% of the CABG group (P = 0.005). The benefit of CABG was driven by superior outcomes in both rates of death from any cause (10.6 vs 14.9%; P = 0.049) and MI (6.0 vs 13.9%; P < 0.001), but at the cost of a higher risk of stroke in the CABG group (5.2 vs 2.4%; P = 0.03). And it is important to appreciate that this benefit of CABG over PCI was still evident although all patients were receiving aggressive medical therapy.

It is also worth noting the relative risk of non-fatal stroke between CABG and PCI was 2.41 at 1 year, narrowing to 1.72 at 5 years [5]. The absolute clinical difference in stroke rates between CABG and PCI was actually small, being 2.1% (30 of 1444) and 0.82% (12 of 1471), respectively, at 1 year and 4.8% (65 of 1344) and 2.8% (42 of 1500) at 5 years. The early difference in stroke is almost certainly a consequence of the very well-recognized perioperative risk of stroke with CABG, with subsequent rates being more similar between the interventions. The same phenomenon was observed in the SYNTAX trial with CABG patients receiving less in the way of single and dual anti-platelet medication in the postoperative period [5].

Are the results of the FREEDOM trial consistent with other evidence? The answer is overwhelmingly, yes, from several other sources. Probably, the second-most definitive piece of evidence regarding the relative benefits of interventions in patients with diabetes is a subset analysis of the collaborative analysis of individual patient data from 7812 patients from 10 trials, of whom 1243 had diabetes, by Hlatky and co-workers. At a median follow-up of 5.9 years, mortality was substantially lower in the CABG group than in the PCI group (hazard ratio [HR]: 0.70, 95% confidence interval [CI]: 0.56–0.87) [6].

Since this analysis, several other pieces of data have emerged supporting the use of CABG rather than PCI in patients with diabetes. In the BARI 2D trial, 2368 patients with both type 2 diabetes and CAD were randomized to intensive medical therapy alone or to additionally undergo either prompt revascularization with PCI or CABG, according to the preference of the treating physician [7]. At 5 years, there was no significant difference in the composite primary end point between the PCI and medical therapy groups. In contrast, in the CABG group, the rate of major cardiovascular
events was significantly lower in the revascularization group (22.4%) than in the medical therapy group (30.5%, \( P = 0.01 \)), with non-significant reductions in mortality, MI and repeat revascularization. However, it should also be acknowledged that the severity of CAD in both the PCI and CABG groups was relatively modest, as only 50% of CABG patients had three-vessel CAD and only 20% proximal left anterior descending CAD; patients with more severe CAD as in the FREEDOM trial might be expected to derive greater benefit from revascularization.

In the CARDia trial [8], 510 diabetic patients with multivessel or complex single-vessel CAD were randomized to PCI or CABG. The trial was terminated early because of poor recruitment. The primary outcome was a composite of all-cause mortality, MI and stroke, and the main secondary outcome included the addition of repeat revascularization to the primary outcome events. At 1 year of follow-up, the composite rates of death, MI and stroke were 10.5% in the CABG group and 13.0% in the PCI group (HR: 1.25, 95% CI: 0.75–2.09, \( P = 0.39 \)), all-cause mortality rates were 3.2 and 3.2% and the rates of death, MI, stroke or repeat revascularization were 11.3 and 19.3% (HR: 1.77, 95% CI: 1.11–2.82, \( P = 0.02 \)), respectively. While the publication of the 5-year results is awaited, it must be emphasized that the survival benefit of CABG usually does not appear until the third year of follow-up.

Of 1800 patients in the SYNTAX trial, 452 had diabetes [9]. In this subgroup, 5-year rates of major adverse cardiac or cerebrovascular events (MACCE) were significantly higher for PCI vs CABG (46 vs 29%, \( P < 0.001 \)) and repeat revascularization (35 vs 15%, \( P < 0.001 \)). While there was no statistically significant difference in the individual components of MACCE because of relatively small numbers, death (PCI: 19.5% vs CABG: 12.9%; \( P = 0.065 \)) and MI (PCI: 9.0% vs CABG: 5.4%; \( P = 0.20 \)) in CABG while stroke was lower with PCI (PCI: 3.0% vs CABG: 4.7%; \( P = 0.34 \)).

Evidence from prospective registries also supports the use of CABG rather than PCI in patients with diabetes and multivessel CAD [10]. In a large regional database of 7159 consecutive patients with diabetes who underwent coronary revascularization in northern New England 2766 (38.6%) were similar to the patients randomized in the BARI trial. Of this cohort, 736 underwent PCI and 2030 underwent CABG. After adjusting for differences in baseline clinical characteristics, PCI resulted in significantly greater mortality than CABG (HR: 1.49; 95% CI: 1.02–2.17; \( P = 0.037 \)). The mortality risk was greater with PCI in 1251 patients with 3VD (HR: 2.02; 95% CI: 1.04–3.91; \( P = 0.038 \)) than among 1515 patients with 2VD (HR: 1.33; 95% CI: 0.84–2.1; \( P = 0.21 \)).

Immediately, and somewhat predictably, some in the interventional cardiology community have disparaged the results of the FREEDOM Trial with the perennial statement ‘but now we have a newer stent’. This emphasizes the recurrent history of PCI, from plain old balloon angioplasty to bare metal stents and then to drug-eluting stents, that the documented inability of stents to equal the clinical and survival benefits of CABG has always met with the response that a newer generation of stents is the answer. It also illustrates the misunderstanding of the different physiological achievements of both interventions. The major advantage of CABG, and particularly with the use of both internal mammary arteries [11], is that by placing bypass grafts to the mid-coronary vessel, this not only makes the complexity of the proximal lesion irrelevant but also offers prophylaxis against the development of further proximal disease. In contrast, stents can only deal with suitable localized proximal lesions, but this benefit can be nullified by the development of disease proximal to, within or immediately distal to the stent.

The strength of evidence in favour of CABG should underpin the decision recommendations of the multidisciplinary Heart Team and new guideline recommendations. The preponderance of evidence in favour of CABG can also give considerable reassurance to patients and their physicians in recommending this as the optimal revascularization technique in patients with diabetes and multivessel CAD who merit intervention and are at low risk for surgery and receptive to this option. In patients who are high risk for, or refuse surgery, or have low-severity CAD, PCI remains an attractive option.

REFERENCES