Determining the Most Appropriate Mode of Coronary Artery Revascularisation in Patients With Diabetes

Ehrin J Armstrong and Stephen W Waldo

Veterans Affairs Eastern Colorado Healthcare System, University of Colorado, Denver, CO, USA

Abstract

Obstructive coronary artery disease is a common cause of morbidity and mortality among patients with diabetes mellitus (DM). Previous research has demonstrated that the clinical sequelae of coronary artery disease remains the most common cause of death in this population. As a result numerous observational studies and randomised clinical trials have evaluated the timing and mode of coronary artery revascularisation within this population. In this review, we survey the currently available data informing the indications and optimal method of coronary revascularisation for diabetic patients.

Keywords

Diabetes, coronary artery disease, coronary artery bypass grafting, percutaneous coronary intervention

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Correspondence: Ehrin J Armstrong, MD, MSc, VA Eastern Colorado Healthcare System, Division of Cardiology, University of Colorado School of Medicine, 12605 East 16th Avenue, 3rd Floor, Aurora, CO 80045, USA. E: ehrin.armstrong@gmail.com

Patients with diabetes mellitus (DM) have an increased prevalence of coronary artery disease (CAD) and are more likely to require coronary revascularisation than patients without DM.¹ Similar to the general population, CAD remains the most frequent cause of death among patients with DM.² As the prevalence of DM continues to rise worldwide, the appropriate management and method of revascularisation for diabetic patients will become an increasingly important clinical decision point. In this review, we discuss current data regarding the indications and optimal method of coronary revascularisation among patients with DM.

Decision to Perform Revascularisation

As with the general population, patients with DM and CAD may present with asymptomatic ischaemia, stable angina or acute coronary syndromes. The clinical presentation and severity of symptoms significantly influences the decision to perform coronary artery revascularisation, as well as the relative timing of such a procedure.

Although patients with DM have a higher prevalence of CAD, the majority of patients are asymptomatic before presenting with a myocardial infarction or other cardiovascular event.³ Numerous studies have therefore investigated the use of routine screening for CAD among diabetic patients that do not have overt symptoms. The Detection of Ischaemia in Asymptomatic Diabetics (DIAD) study investigated routine screening for coronary ischaemia using myocardial perfusion imaging among asymptomatic diabetic patients.⁴ During a mean follow-up of 4.8 years, the overall cardiac event rate was only 2.9 % with an event rate of 2.7 % in the screened group and 3.0 % in the unscreened group. The overall rate of revascularisation was also low at 5.5 % in the screened group and 7.8 % in the unscreened group. Similarly, the Screening For

Asymptomatic Obstructive Coronary Artery Disease Among High-Risk Diabetic Patients Using CT Angiography, Following Core 64 (FACTOR 64) trial randomised patients with diabetes and no symptoms of CAD to screening coronary computed tomography angiography (CCTA) or usual care.⁵ After a mean follow-up of 4.0 years there was no significant difference in event rates between the screened and unscreened groups (6.2 versus 7.6 %). Randomisation to CCTA resulted in only 36 (8 %) coronary angiographies and 26 (5.8 %) coronary revascularisations. Together these two large randomised trials do not support a strategy of routine testing for CAD among asymptomatic diabetic patients.

Among diabetic patients with symptomatic stable CAD, the decision to pursue revascularisation with either a percutaneous or surgical approach was studied in the Bypass Angioplasty Revascularisation Investigation in Type 2 Diabetes (BARI 2D) study.⁶ In that trial diabetic patients with stable CAD were randomised to either optimal medical therapy with immediate percutaneous or surgical revascularisation at the discretion of the investigator or optimal medical therapy alone. At 5 years there was no difference in overall mortality between the two groups, although the rate of subsequent revascularisation in the medical therapy group was 38 % at 5 years. These results suggest that immediate revascularisation is not necessary among patients with DM and stable CAD in the absence of severe anginal symptoms, while recognising that a significant percentage of patients will eventually require revascularisation due to worsening of their symptoms. For this reason, all patients with DM and unrevascularised CAD should be closely monitored for disease progression.

Approximately 30 % of patients presenting with an acute coronary syndrome (ACS) have DM and a larger percentage of patients present

with previously undiagnosed diabetes and/or hyperglycaemia.^{7,8} In large-scale clinical trials of revascularisation for ACS, patients with DM have demonstrated a similar relative benefit (and larger absolute benefit) compared to the overall clinical trial population studied.⁹ For this reason, diabetic patients presenting with ACS should undergo an early invasive strategy to determine the most appropriate method of revascularisation.

Method of Revascularisation

A number of studies have investigated the outcomes of coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI). The majority of these trials have enrolled diabetic patients with multivessel CAD and stable angina, although some studies have included patients with unstable angina or non-ST-elevation myocardial infarction (MI).¹⁰ Among patients with single-vessel or two-vessel CAD and DM, the majority of guidelines support a strategy of PCI. The exception to this may be the presence of high-grade ostial/proximal left anterior descending (LAD) coronary artery stenosis where a left internal thoracic artery to LAD bypass may provide a mortality benefit relative to angioplasty among diabetic patients. Those results are based on the BARI study, which included a large cohort of diabetic patients with multivessel CAD and at 10 years of follow-up randomisation to CABG was associated with reduced mortality and myocardial infarction compared to coronary angioplasty.¹¹ However, that study and other smaller, contemporaneous trials utilised angioplasty or bare metal stents, making it difficult to extrapolate such findings to contemporary medical practice. In general, those trials reported overall higher rates of revascularisation with diabetic patients relative to the overall study population but no single trial was powered to examine outcomes specific to diabetic patients.

Recent meta-analyses and observational studies comparing surgical and percutaneous revascularisation for isolated proximal LAD disease did not find any difference in 3-year mortality, albeit with higher rates of repeat revascularisation in patients treated with PCI (13 versus 7 %).^{12,13} Although these analyses were not specifically limited to diabetic patients, such studies suggest that PCI and CABG may have clinical equipoise in the setting of diabetic patients with isolated proximal LAD disease and/or proximal LAD disease with disease in second coronary artery amenable to percutaneous revascularisation.

The Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) trial was a multinational, multicentre randomised trial of 1,800 patients with three-vessel or left main CAD amenable to surgical or percutaneous revascularisation who were randomised to CABG or PCI.¹⁴ The stent used in this study was the TAXUS paclitaxel drug-eluting stent, which was a first-generation drug eluting stent (DES) no longer used widely in clinical practice. Relative to the overall cohort, the subgroup of patients with DM had overall higher event rates after either CABG or PCI. CABG was associated with lower 5 year major adverse cardiovascular events (MACE), but patients with a lower atherosclerotic burden assessed by the SYNTAX score had similar outcomes with PCI or CABG.¹⁵

More recently, the Randomised Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease (BEST) trial randomised 880 patients with multivessel CAD to CABG versus PCI with everolimus-eluting stents.¹⁶ At short-term follow-up of 2 years, the rate of death, MI or target vessel revascularisation occurred in 11.0 versus 7.9 % of patients randomised to PCI versus CABG. At a longer-term median follow-up of

4.6 years, these events occurred in 15.3 % of patients that underwent percutaneous revascularisation and 10.6 % of patients that underwent surgical revascularisation. These endpoints were primarily driven by an increased rate of repeat revascularisation among patients randomised to PCI, as there was no significant difference in the safety endpoint of death, MI or stroke. Approximately 40 % of the patients enrolled in the trial were diabetic, and subgroup analysis suggested that patients with DM derived significantly greater benefit from CABG relative to the non-diabetic subgroup (HR 1.07, 95 % CI [0.65–1.76] for non-diabetics, versus HR 2.24, 95 % CI [1.25–4.0] for diabetics).

Consistent with the results of the BEST trial, an observational study of CABG versus PCI with everolimus-eluting stents for diabetics with multivessel disease found that PCI was associated with a similar long-term rate of death (10.5 versus 10.3 %), a lower rate of stroke (2.9 versus 3.9 %), a higher rate of MI (6.4 versus 4.1 %), and a higher rate of repeat revascularisation (22 versus 10.4 %).¹⁷ Interestingly, the higher rate of MI after PCI was not observed among patients who underwent complete revascularisation. These findings suggest that complete revascularisation with PCI in diabetic patients may result in similar long-term outcomes to CABG.

The The Future REvascularization Evaluation in patients with Diabetes mellitus: optimal management of Multivessel disease trial (FREEDOM) trial specifically examined the outcomes of diabetic patients with multivessel CAD randomised to CABG versus PCI.¹⁸ At 5 years of follow-up, the endpoints of all-cause mortality (10.9 versus 16.3 %) and MI (6.0 versus 13.9 %) were significantly lower among patients randomised to CABG. Secondary analysis also did not find any interaction between the SYNTAX score and outcomes, suggesting that the benefit of surgical revascularisation may be independent of anatomic complexity among diabetic patients with multivessel CAD. Similar results were observed in a smaller randomised trial of Veterans (VA CARDS) with diabetes and multivessel CAD, which was terminated early due to significantly higher event rates in the group randomised to PCI.¹⁹ Although the FREEDOM and Veterans Administration Coronary Artery Revascularization in Diabetes (VA CARDS) trials provide compelling evidence for surgical revascularisation over PCI among diabetic patients with multivessel CAD, several limitations of the study populations should be considered. First, the majority of patients in the trials were low-risk for surgery and had preserved ejection fraction; whether these findings apply to patients at higher surgical risk remains uncertain. Second, first-generation DES were utilised in the majority of patients; second-generation DES, which have improved outcomes among diabetic patients, may narrow the outcomes gap among diabetic patients.

Based on these results of recent studies, diabetic patients with multivessel CAD who are operative candidates should be evaluated by a multidisciplinary heart team to determine the optimal therapeutic approach, with a goal towards complete revascularisation. Given the long-term mortality benefit observed with CABG in the FREEDOM trial, patients who are younger and/or low-risk for surgery should be referred for surgical revascularisation. As stent technologies continue to evolve, future studies will continue to evaluate whether the therapeutic gap between CABG and PCI will narrow for diabetic patients.

Stent Type and Outcomes Among Patients With Diabetes

Drug eluting stents (DES) are associated with significantly decreased rates of restenosis and target lesion revascularisation for both

diabetic and non-diabetic patients. Whether specific DES types have a treatment advantage among patients with DM remains an active area of investigation.

Among first generation DES, both paclitaxel eluting stents (PES) and sirolimus eluting stents (SES) were shown to reduce rates of repeat revascularisation and major adverse cardiovascular events relative to BMS in diabetic patients.^{20,21} In a mixed treatment meta-analysis of stent types, SES were associated with reduced rates of major adverse cardiovascular events relative to PES, suggesting that limus-eluting DES may be preferred among patients with DM.²²

Two types of zotarolimus eluting stents (ZES) have been studied in diabetic patients. The initial ZES (Endeavor®, Medtronic, Inc) had a short drug elution time and was associated with higher rates of restenosis than contemporaneous stents. The subsequent Resolute® ZES (R-ZES) has a longer elution time of zotarolimus, thereby more effectively inhibiting restenosis. The R-ZES was the first DES specifically approved for use in diabetic patients. This approval was based on a predetermined performance goal of a 14.5 % 1-year rate of target vessel failure (TVF). In a large clinical trial, R-ZES in diabetic patients was associated with a significantly lower rate of TVF (7.8 %) relative to the performance goal.²³ Other studies have suggested similar clinical outcomes between R-ZES and everolimus eluting stents (EES) in real-world clinical settings.²⁴

EES are associated with reduced rates of restenosis and target lesion revascularisation relative to first-generation DES. In angiographic and intravascular ultrasound studies of EES and PES in diabetic patients, EES were associated with less neointima formation and lower rates of restenosis.^{25,26} Similarly, studies of EES versus SES in diabetic patients found that EES are associated with lower rates of restenosis than SES.²⁷ In comparison, a pooled analysis of randomised studies found no difference in efficacy or safety of EES versus PES among

diabetic patients, suggesting that EES may not have significant benefit compared to PES.²⁸

Based on conflicting data with outcomes of different DES types among patients with diabetes, the recently reported Taxus Element versus Xience Prime in a Diabetic Population Taxus Element versus Xience Prime in a Diabetic Population (TUXEDO)-India study randomised 1,830 patients with diabetes to PCI with PES or EES.²⁹ At 1 year, patients randomised to paclitaxel had significantly higher rates of target vessel failure (5.6 versus 2.9 %) and stent thrombosis (2.1 versus 0.4 %). These results suggest that EES are significantly favoured over PES among patients with diabetes. Overall, clinical studies have demonstrated that improvements in stent design have been associated with reduced rates of target lesion revascularisation and reduced stent thrombosis among diabetic patients. Recent randomised data suggest that EES are favored over PES; other related drugs such as zotarolimus likely have a similar anti-restenotic effect. Future developments in stent technologies for treatment of diabetic patients will include clinical outcomes of bioresorbable scaffolds, which could be a useful treatment for diffuse disease or treatment of LAD disease among patients who may require future therapeutic options.

Conclusion

Coronary artery disease remains highly prevalent among diabetic patients. Research has demonstrated that complete surgical revascularisation is appropriate for symptomatic patients given the lower rate of repeat revascularisations needed, though advances in percutaneous techniques and stent technologies make percutaneous revascularisation an increasingly attractive option for this population. Among currently available stents, everolimus eluting stents are associated with the lowest rates of target lesion revascularisation and stent thrombosis among diabetic patients. Future studies will evaluate newer stent design technologies in diabetic patients, including bioresorbable polymer and bioresorbable scaffold technologies. ■

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