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Stents, surgery, and optimal medical therapy in diabetes

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Abstract

The successful management of coronary artery disease in diabetic patients requires an understanding of the differences between diabetic and nondiabetic coronary disease with respect to pathophysiology and angiographic features. The impact of lesion complexity and subsequent completeness of revascularization must be considered, along with the impact of stent selection or graft use and the mode of presentation. While current evidence favors surgical revascularization in stable patients, with multivessel disease, especially those with complex angiographic coronary disease, the optimal strategy in patients presenting emergently with an acute coronary syndrome, particularly with ST-segment elevation on the electrocardiogram, requires clarification. This review summarizes the role of coronary stenting, surgery, and optimal medical therapy in the treatment of coronary artery disease in patients with diabetes in the contemporary era. ■ *Heart Metab*. 2015;68:9-14

Keywords: coronary artery bypass graft surgery; coronary heart disease; diabetes mellitus; optimal medical therapy; percutaneous coronary intervention

Diabetes mellitus (DM) is a powerful independent risk factor for coronary heart disease (CHD) and is increasing worldwide; approximately 25% of patients undergoing invasive angiographic assessment have DM.[1-3] Diabetic patients more commonly have complex coronary artery disease with diffuse plaques involving mid and distal arterial branches and more frequently have multivessel disease (MVD). It is important to emphasize that both DM and MVD are associated with increased major cardiac events in patients with ischemic heart disease.[4-6]

Revascularization is indicated in patients with stable CHD who have persistence of symptoms despite medical treatment. It is also indicated in stable CHD when there is inducible ischemia on noninvasive (or invasive) testing and/or significant left ventricular impairment.[7] There is a clear benefit with early revascularization in non–ST-segment elevation acute coronary syndromes (NSTEACS). In patients with ST-segment elevation myocardial infarction (STEMI), emergency reperfusion improves mortality rates. The optimal management of CHD in patients with DM also requires combination pharmacotherapy to ensure good long-term outcomes and risk prevention.

Pathophysiological changes evident in diabetic patients

The patterns of coronary artery disease in diabetes differ from those in nondiabetic patients. Necrotic cores

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Abbreviations

BARI: Bypass Angioplasty Revascularization Investigation; **BARI 2D:** Bypass Angioplasty Revascularization Investigation 2 Diabetes; **BMS:** bare-metal stent; **CABG:** coronary artery bypass graft; **CARDia:** Coronary Artery Revascularization in Diabetes trial; **CHD:** coronary heart disease; **CI:** confidence interval; **COURAGE:** Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation; **CVA:** cerebrovascular accident; **DAPT:** dual antiplatelet therapy; **DES:** drug-eluting stent; **DM:** diabetes mellitus; **FAME:** Fractional flow reserve versus Angiography for Multivessel Evaluation; **FREEDOM:** Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease; **HR:** hazard ratio; **LAD:** left anterior descending; **LIMA:** left internal mammary artery; **MACCE:** major adverse cardiac and cerebrovascular event; **MI:** myocardial infarction; **MVD:** multivessel disease; **NSTEACS:** non–ST-segment elevation acute coronary syndromes; **NSTEMI:** non–ST-segment elevation myocardial infarction; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **RCT:** randomized controlled trials; **RR:** repeat revascularization; **STEMI:** ST-segment elevation myocardial infarction; **SYNTAX:** SYNergy between percutaneous intervention with TAXus and cardiac surgery trial; **VA CARDS:** Veterans Affairs Coronary Artery Revascularization in Diabetes study

in atherosclerotic plaques are larger and adaptive vascular remodeling is decreased. Diabetic patients also have accelerated plaque maturation and increased plaque instability mediated in part by endothelial dysfunction and a complex cascade of cytokines including nuclear factor–κB, a key protein complex controlling progression of coronary artery disease. In addition, patients with diabetes are more vulnerable to coronary events due to an increased prothrombotic milieu; they demonstrate abnormal platelet function and increased glycoprotein receptor Ib and IIb/IIIa expression, which augments von Willebrand factor and platelet-fibrin interactions. Increased factor VII, thrombin, and tissue factor concentrations, and protein C activity also augment thrombotic risk.[4,8-10] Microvascular dysfunction and cardiac energy metabolism are also likely to contribute significantly to the increased risk of acute coronary syndrome for DM patients.

Coronary angiographic patterns associated with diabetes

These pathophysiological changes result in functionally significant stenoses, often angiographically evident as MVD, commonly involving distal arterial branches. This complex diffuse disease impacts upon the success of revascularization procedures. Diffuse disease is more likely to require deployment of multiple stents in long segments of small-caliber vessels and incomplete revascularization is more common both percutaneously and surgically, as a site suitable for grafting may be absent. Surgical revascularization is favored in triple-vessel disease and is recommended in diabetic patients.[7] Much of the benefit of coronary artery bypass grafting (CABG) revascularization is seen primarily with arterial graft conduits.[3,11] Diabetic patients have less frequently received "gold standard" surgery with bilateral mammary artery grafting, due to the risks of sternal dehiscence seen in diabetic patients.[12,13]

Coronary revascularization in patients with diabetes mellitus

The majority of pertinent randomized controlled trials (RCT) comparing revascularization strategies in diabetic patients alone have been reported in the last 5 years (*Table I*), though subgroup analysis of the BARI trial (Bypass Angioplasty Revascularization Investigation)[14] 15 years earlier reported an increased vulnerability of diabetic patients to late events after percutaneous coronary intervention (PCI). Key trials informing practice include SYNTAX,[15] CARDia,[16] VA CARDS,[17] and FREEDOM[3]; respectively, the SYNergy between percutaneous intervention with TAXus and cardiac surgery trial, the Coronary Artery Revascularization in Diabetes trial, the Veterans Affairs Coronary Artery Revascularization in Diabetes Study, and the Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease trial.

Post hoc analyses from the BARI trial suggested a mortality benefit for diabetic patients with MVD with surgical revascularization, a benefit not evident in non-diabetic patients. The BARI trial was a large (n=1829) North American RCT performed in the pre-stent era where PCI patients were treated with balloon angioplasty. Rates of 5-year survival in patients with medically treated diabetes (n=357) were 65.5% for PCI and

80.6% for CABG (*P*=0.003), while in the nondiabetic patients (81%) 5-year survival was the same.[14]

The SYNTAX trial compared PCI with paclitaxel drug-eluting stents (DES) with CABG in patients with MVD and or left main stem disease, enrolling 1800 patients, 452 of which had diabetes. First-generation stents were used and arterial graft use was high (97.3%).[15] Overall, authors found both diabetic and nondiabetic patients had higher rates of major adverse cardiac and cerebrovascular events (MACCEs) and repeat revascularization (RR) at 5 years with PCI, particularly where disease was anatomically complex. In the prespecified subgroup analysis of diabetic patients, MACCE rates at 5 years were 46.5% for PCI vs 29.0% for CABG (*P*≤0.001), and RR rates were also significantly higher with PCI vs CABG (35.3% vs 14.6%; *P*<0.001). No significant difference was seen in the composite of death/stroke/myocardial infarction (MI) or in these components individually.[18]

The SYNTAX trial had a lasting impact not only because of the data generated, but also because of the development and use of the SYNTAX score, an objective scoring system to grade anatomical lesion complexity in the entire coronary artery tree. Prior to the SYNTAX score, authors primarily used the number of diseased vessels to describe the extent of coronary disease, or a modified American College of Cardiology (ACC)/American Heart Association (AHA) score to divide individual lesion complexity into 4 groups. The SYNTAX score evaluates the complexity and site of each lesion in the whole coronary tree; lesions are weighted for their site and territory within the coronary tree (*Figure 1*), allowing comprehensive evaluation of the territories at risk. This development is particularly important in patients with complex disease, such as diabetes, and can be used in selection of the method of revascularization, and to assess the likelihood of adverse outcomes and the impact of incomplete revascularization.

The first RCT specifically looking at diabetic patients, CARDia, enrolled patients with both MVD and complex single-vessel left anterior descending (LAD) artery disease. This was a small multicenter (n=510) trial from the United Kingdom. Patients were treated with bare-metal stents (BMS) and first-generation drug-eluting stents (DES) as they became available. This noninferiority trial was acknowledged by authors to be underpowered. It used a combined primary end point of all-cause mortality, MI, and stroke and at 1-year follow-up found event rates of 10.5% after CABG and 13.0% after PCI (*P*=0.39). No difference in all-cause mortality or MI was evident, but repeat revascularization was more frequent in PCI patients (11.8 vs 2%; *P*<0.001), and major bleeding was more common in CABG patients (6.1% vs 1.2%; *P*=0.009), as was nonfatal cerebrovascular accident (CVA) (2.8% vs 0.4%; *P*=0.066).[16]

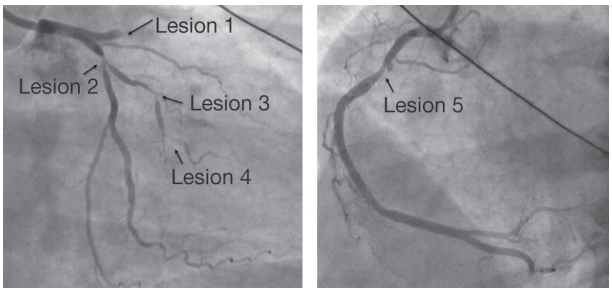

Fig. 1 *Illustrative angiogram with SYNTAX score. This diabetic patient with proximal multivessel disease, presenting with an ST-segment elevation myocardial infarction due to an occluded culprit left anterior descending artery, has an overall SYNTAX score of 34.5. Lesion 1 contributes 20.5 points weighted for a new total occlusion with thrombus in the proximal left anterior descending artery. Lesion 2, 8 points for a bifurcation lesion involving the proximal circumflex and obtuse marginal branches. Lesions 3 and 4, 2 points each for obtuse marginal branch stenoses. Lesion 5, 2 points for proximal right coronary artery stenosis.*

	n	Diabetes	Stent type	Primary outcome	Death	MI	Repeat revascularization	MACCE	CVA
FREEDOM*	1900	100%	DES	Death + MI + CVA*	10.9% vs 16.3%	6% vs 13.9%	4.8%* vs 12.6%*	11.8%* vs 16.8%*	5.2% vs 2.4%
VA CARDS	198	100%	DES	Death + MI	5% vs 21%	15% vs 6.2%	NS	NA	NS
CARDia	510	100%	BMS + DES	Death +MI +CVA	NS	NS	2% vs 11.8%	11.3% vs 19.3%	2.8% vs 0.4%
SYNTAX**	1800	25%	DES	MACCE	NS	NS	14.6% vs 35.3%	29% vs 46.5%	NS
BARI**	1825	19.5%	POBA only	Death	19.4% vs 34.5%	NA	NA	NA	NA

Table I *Summary of randomized controlled trials comparing coronary artery bypass grafting vs percutaneous revascularization respectively.*
Abbreviations: *CVA, cerebrovascular accident; BMS, bare-metal stent; DES, drug-eluting stent; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NA, not applicable; NS, not significant; POBA, plain old balloon angioplasty. *5-Year follow-up data shown, with the exception of repeat revascularization and MACCE, where 1-year data only are reported. The primary composite outcome at 5 years was 18.7% vs 26.6%. **Results in the table show results for diabetic patients only.*

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VA CARDS was another small underpowered RCT (n=198), including isolated proximal LAD artery disease or LAD artery disease with coexisting MVD; sirolimus or paclitaxel DES were used. The trial was terminated early and reported the combined primary end point of all-cause mortality and MI. At 2-year follow-up, there was no difference between groups; unsurprisingly, repeat revascularization did not differ significantly between groups. Mortality was lower in surgically treated patients (5% vs 21%; hazard ratio [HR], 0.30; 95% confidence interval [CI], 0.11-0.80). However, nonfatal MI was lower in patients treated by PCI (6.2% vs 15%; HR, 3.32; 95% CI, 1.07-10.30). VA CARDS was the only trial to mandate serial electrocardiograms and nuclear scans post revascularization, perhaps explaining why it found increased MI in surgical patients. These investigations detected clinically silent MI, probably masked by postsurgical analgesia, as all detected silent MIs were observed in surgically treated patients and represented 30% of all nonfatal MIs in CABG patients.[17]

The most important RCT is the FREEDOM trial, which enrolled 1900 patients with diabetes with MVD, but without left main stem disease. While second-generation DES were used the last year of randomization, most stented patients received first-generation DES; 95% of patients had ≥1 mammary artery conduit in the CABG group. At 5-year follow-up, FREEDOM found lower event rates after CABG for the primary end point (composite of death, MI, and CVA) (18.7% vs 26.6%; *P*=0.005), individual events of death (10.9% vs 16.3%; *P*=0.049), MI (6.0% vs 13.9%; *P*<0.001), whereas CVA was more frequent post-CABG (5.2% vs 2.4%; *P*=0.03). Repeat revascularization and MACCE were not reported at 5-year follow-up; at 1 year they were 4.8% vs 12.6% (*P*<0.001) and 11.8% vs 16.8% (*P*=0.004) respectively. The FREEDOM trial led to changes in guidelines with a class IA recommendation for surgical treatment in patients with diabetes with MVD.[3]

The hypothesis generated by the BARI trial, that a left internal mammary artery (LIMA) conduit on the LAD coronary artery was prognostically protective took 2 decades for the FREEDOM trial to confirm. On analysis of patients with MVD *not* involving the LAD artery, and thus not requiring a LIMA to LAD artery graft, HRs approached 1 with broad CIs, suggesting the benefits of surgical revascularization are smaller,[3] though when disease severity was divided by tertiles of the SYNTAX score, there was no *P*-value for interaction.

Noncomplex coronary disease

The majority of research comparing CABG with PCI focuses on triple-vessel disease. Noncomplex and single-vessel disease is predominantly treated by PCI. However, conflicting evidence exists in noncomplex MVD. Data from the SYNTAX trial[18] found that patients with diabetes and SYNTAX scores <23 had similar combined rates of death, MI, and stroke (20.1% for CABG and 19.4% for PCI; *P*=0.79). Where the disease was complex (SYNTAX score ≥ 33), in patients with diabetes, the data strongly favored CABG. SYNTAX authors concluded that differences in MACCE were driven primarily by increased rates of further revascularization; this difference is greater in diabetic subgroups. However, subgroup analysis for the FREEDOM trial using SYNTAX scores found the combined end point death/MI and stroke in lower-SYNTAX-score patients were also significant (18.7% of CABG and 26.6% for PCI; *P*=0.005).[3] A meta-analysis[6] found that further revascularization was only increased in diabetic patients where complex lesions were treated; in noncomplex disease, rates were similar in patients with and without DM.

Optimal medical treatment in diabetic patients with coronary disease

The management of diabetes and coronary disease also must involve optimal medical therapy (OMT). Recommendations include insulin sensitization or insulin provision, statins, β-blockade, angiotensin-converting enzyme (ACE) inhibition/angiotensin II receptor blocker (ARB) use, and aspirin (or dual antiplatelet therapy [DAPT] with $P2Y_{12}$ inhibitors, where an ischemic event has occurred or percutaneous revascularization has been performed).[7,19] The BARI 2D (diabetes) trial, investigated whether insulin sensitization or insulin provision results in superior outcomes for patients with coronary artery disease. This large trial including 2368 patients with type 2 diabetes and stable coronary disease found no significant difference in survival alone or in freedom from major cardiac events between insulin sensitization and insulin provision.[20]

OMT in the setting of STEMI, non–ST-segment elevation myocardial infarction (NSTEMI), and unstable angina should be used *in conjunction* with revascularization to improve cardiovascular outcomes, and

benefits are well established. OMT as an *alternative* to revascularization should only be considered in limited settings, such as stable angina. In diabetic patients, the clinician should be particularly cognizant of clinically silent, but significantly unstable, coronary artery disease seen in some diabetic patients, and objectively establish the burden of disease before considering OMT alone. It should be noted that recent and contemporary major trials of OMT vs PCI, such as COURAGE (Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation),[21] BARI 2D,[20] FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation), and FAME-2,[22,23] required angiography to define the burden of disease before including patients. Blind selection of OMT is not supported by these trials. Revascularization is usually indicated in patients with stable CHD, when there is inducible demonstrable ischemia on noninvasive imaging, or invasive functional assessment of stenosis by fractional flow reserve (FFR), and/or significant left ventricular impairment.[7,24]

Unanswered questions

The impact of incomplete revascularization

In trials comparing CABG and PCI, a significant disparity is seen in completeness of revascularization favoring surgically treated patients. The importance of complete revascularization has been acknowledged in surgical literature for some time.[25] There is growing interest in both defining and achieving more appropriate levels of percutaneously achieved complete or near-complete revascularization.[26-28] No large multicenter RCT has assessed completeness of revascularization between techniques, or tested whether complete revascularization is superior to incomplete revascularization. However, retrospective subgroup analysis using the residual SYNTAX score to define the degree of incomplete revascularization is increasingly being employed to address this question. Defining the impact of incomplete revascularization in NSTEMI and STEMI populations may further explain poorer long-term outcomes with PCI seen in DM patients.

Second-generation DES vs CABG

BMS are associated with late restenosis due to neointimal hyperplasia. Diabetes is known to be a significant risk factor for restenosis. As a result, DES became the preferred stent choice for diabetic patients. First-generation DES were found to have significant problems with stent thrombosis, a rare but often fatal late complication, thought to be overcome with second-generation DES. None of the landmark trials listed above exclusively used second-generation DES. A recent meta-analysis found no statistically significant difference in revascularization between cobalt-chromium everolimus-eluting stents (second-generation DES) and CABG and no significant increase in mortality in diabetic patients,[29] suggesting contemporary trials comparing revascularization techniques are required.

Diabetes and STEMI in MVD

Most revascularization trials only included stable patients with angina and NSTEACS. The relevance to patients who would not have met these inclusion criteria remains uncertain and is not guided by level A or B evidence.[30] The treatment of STEMI patients in emergent situations is predominantly percutaneous, to ensure timely reperfusion. However, the FREEDOM results have generated uncertainty regarding the best management for nonculprit disease in patients with DM and MVD, especially when the infarct-related artery is the LAD artery. The future treatment of nonculprit disease must be considered at the time of the index admission, because uninterrupted DAPT is recommended for 3-12 months. If the nonculprit coronary disease still meets FREEDOM entry criteria, nonemergent CABG should be considered rather than further PCI.

Conclusions

The treatment of patients with diabetes and coronary disease, identified nonemergently at angiography, should have CABG if they have MVD, especially with LAD artery involvement. However, in FREEDOM, there was no interaction between the SYNTAX score and the benefit of CABG over PCI with DES. OMT involves 4-5 secondary prevention therapies recommended for all patients with stable CHD, together with insulin sensitization and insulin provision. However, there are unanswered questions about the optimal procedural management of patients presenting with anterior STEMI undergoing successful primary PCI. ■

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