

The advantage of surgical revascularization in diabetic patients with multivessel disease: More arterial conduits, more benefit



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Diabetes mellitus (DM) in North America is a national health crisis, expected to affect 36 million people in the United States alone in 2030, almost twice as many than in 2010.¹ Patients with established coronary artery disease (CAD) who also have DM carry a worse prognosis compared with patients without DM.² In addition, CAD accounts for up to 75% of deaths in diabetic patients, and more than 30% of patients presenting with an acute coronary syndrome have DM.³

Diabetic patients have constituted approximately 40% of patients undergoing coronary artery bypass grafting (CABG) since the 2000s, compared with only 7% in the 1970s.⁴ After surgery, patients with DM have worse short- and long-term survivals, in addition to increased immediate postoperative complications such as stroke, renal failure, wound infection, and length of stay.⁴ DM is associated with more rapid progression of disease in saphenous vein grafts and in grafted and nongrafted native coronary arteries.^{5,6}

The evidence is fairly robust with regard to the superiority of CABG over percutaneous coronary intervention (PCI) in patients with DM and multivessel disease (MVD).⁷⁻¹¹ As to the choice of the CABG conduits, in this patient cohort, there are data to suggest long-term benefits of multiarterial grafting (MAG) strategies, primarily based on large observational studies.¹²⁻¹⁵

This review will delineate the pathophysiology and anatomy of CAD in patients with DM, examine the available literature comparing CABG with PCI, and discuss the role of MAG in this patient population.

PATHOPHYSIOLOGY AND ANATOMY: WHY CORONARY ARTERY BYPASS GRAFTING MAKES SENSE

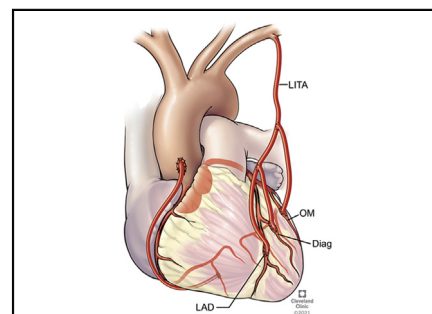
Diabetic atherosclerosis is complex and mainly involves abnormalities in endothelial and vascular smooth muscle cell function. These have been attributed to various metabolic abnormalities, such as hyperglycemia, insulin resistance, and elevated free fatty acid liberation, which contribute to systemic reduction in the bioavailability of nitric oxide and increased oxidative stress.¹⁶

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MAG with composite skeletonized BITA and RA grafts, bypassing diffuse CAD.

CENTRAL MESSAGE

MAG in appropriately selected patients with DM and multivessel CAD is associated with improved long-term outcomes.

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See Commentaries on pages 123 and 125.

Studies have consistently shown greater plaque burden, inflammatory content, and calcification in diabetic individuals compared with nondiabetic individuals.¹⁶ Diabetes causes more diffuse coronary disease with a 2-fold higher rate of total occlusions, making PCI difficult if not impossible and surgical revascularization technically more challenging.

Diabetes negatively affects the outcomes of both PCI and CABG. Numerous studies have shown that the risk of stent restenosis is doubled in patients with DM compared with patients without DM, placing them at higher risk for myocardial infarctions and need for repeat revascularizations.^{17,18} The diffuse disease and diminished runoff associated with diabetes are known to negatively affect graft patency rates.¹⁹ Therefore, it is not surprising that insulin-dependent DM was found to affect perioperative outcomes²⁰ and to be one of the predictors of long-term survival after CABG (ASCERT study).²¹

Diabetic patients with CAD are more prone to develop progressive atherosclerotic plaque in the coronary beds.¹⁶ PCI typically addresses the critical flow-limiting lesion, but disease progression in nontreated segments after PCI is an important cause of major adverse cardiovascular events (MACCEs),

providing a rationale for the difference in results observed with short- versus longer-term (>5 years) follow-up studies comparing PCI with CABG.^{22,23}

Most clinically important obstructive lesions occur within the proximal 6 cm of coronary arteries, a distance typically bypassed in a CABG operation.^{22,24} Surgical revascularization protects against progression of native coronary atherosclerosis and de novo lesions by providing unhindered blood flow to the more distal coronary segments that are less likely to be diseased. Thus, CABG provides “surgical collateralization” that can improve survival by preventing future myocardial infarctions.²⁵ This explains the consistent CABG advantage over PCI in patients with MVD and particularly diabetic patients with heavy atherosclerotic burden.

The durability of CABG is determined by long-term graft patency. Vein graft atherosclerosis is usually responsible for late graft failure and is the Achilles’ heel of CABG surgery. On the other hand, the internal thoracic artery (ITA) is rarely affected by atherosclerosis because of its unique biological properties, such as increased nitric oxide levels that may also have a protective effect on native coronary circulation.²⁶⁻²⁹ Although not as resistant to atherosclerosis as ITAs, radial conduits are better than vein grafts and may be associated with similar outcomes to the use of right ITA grafts when supplementing a left ITA to left anterior descending (LAD) artery, even in diabetic patients.^{12,30}

COMPARATIVE STUDIES OF REVASCLARIZATION STRATEGIES

Multiple randomized controlled trials (RCTs) have demonstrated the superiority of CABG over PCI in the treatment of MVD associated with DM.^{8-11,31} The bypass Angioplasty Revascularization Investigation (BARI 1) trial prospectively randomized patients with MVD to PCI or CABG. Although only 82% of patients received an ITA graft, the subgroup with DM had a significantly better 5-year survival with surgery compared with PCI.⁸

The BARI 2 trial randomized patients with both CAD and DM to undergo intense medical therapy alone or with a revascularization strategy (CABG or PCI). A significant finding was MACCE reduction with surgery compared with medical therapy, a finding not seen among those who were selected to undergo PCI.⁹ The lack of the anticipated surgical survival advantage in this study can perhaps be explained, at least in part, by less than optimal use of even a single ITA conduit, in addition to the high prevalence of off-pump cases (36%) with its reported higher rates of incomplete revascularization and lower patency graft rates.³² Other contributing factors include the intermediate follow-up period of an average 5 years, because the survival benefit from surgery is typically seen in the second decade after the index operation.³³⁻³⁵

Insights from the Arterial Revascularization Therapy Study (ARTS) trial on the impact of DM on PCI and surgical treatment of MVD noted that DM was a strong risk factor for

the occurrence of MACCE in the population assigned to PCI but not in the CABG group.³¹ Likewise, the subgroup analysis of diabetic patients with MVD in the SYNTAX trial revealed a significantly higher rate of cardiac deaths of approximately 3 times in the PCI group compared with the CABG cohort.³⁶ Furthermore, a post hoc analysis at 10 years, the Medicine Angioplasty Surgery Study (MASS) II, was conducted of the randomized prospective MASS I trial that compared medical treatment, CABG, and PCI. In the entire surgical group including diabetic patients and nondiabetic patients, 41% received 2 ITAs or radial arteries (RAs); however, 6% received no arterial grafts. Among diabetic patients with MVD, a statistically significant difference was noted in the cardiac mortality rate favoring CABG.³⁷

The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multi-vessel Disease (FREEDOM) trial was the first adequately powered randomized study, in diabetic patients with MVD, to compare CABG with PCI using drug-eluting stents. The FREEDOM follow-up study showed that in patients with DM and MVD, CABG was associated with improved long-term survival and reduction in MACCE at 8 years compared with PCI and drug-eluting stents.^{10,11} In this trial, 94.4% had a left ITA, 12.3% had bilateral ITA (BITA), and 6.4% had left ITA with RA grafts.

Beyond the narrow and selected population of an RCT, a large observational review of real-world practice of patients presenting with an acute coronary syndrome showed that CABG had a 52% long-term mortality reduction and 37% superiority in terms of MACCE outcomes over PCI.³⁸ Likewise, Takagi and colleagues³⁹ reported the outcomes of more than 8000 patients with DM and MVD in a propensity score-matching analysis. They noted that CABG was associated with improved long-term mortality and freedom from MACCE compared with PCI. The cumulative incidence of myocardial infarction was 16.4% among those who received PCI compared with 7.2% in patients who underwent CABG, and repeat revascularization was greater than 3-fold in the PCI group (25.9% vs 7.8%). Of note, 82% in the surgical cohort received 3 or more grafts compared with only 4.6% in the PCI group who had 3 or more vessels stented, which is a reflection of the superior ability of CABG in attaining the important goal of complete revascularization.³⁹

The 2014 American Heart Association/American College of Cardiology guidelines for the revascularization of stable ischemic heart disease recommend that patients with diabetes and complex 3- or 2-vessel disease with proximal LAD artery involvement, who are good surgical candidates, should be treated with CABG (Class I, Level of Evidence: B).³ Similar recommendations were made in the 2018 guidelines of the European Society of Cardiology/European Association for Cardio-Thoracic Surgery in patients with DM and MVD, but with a higher level of

evidence for CABG over PCI (Class I, Level of Evidence: A).⁴⁰

The importance of arterial grafting in reaping an additional survival benefit in CABG cannot be overemphasized. In fact, the survival advantage in the BARI trial was most evident and pronounced in the surgical group subset who received an ITA graft.^{6,8} A recent meta-analysis of RCTs, comparing surgical revascularization with PCI in diabetic patients, found a 33% mortality reduction at 5 years with CABG, despite an arterial bypass use rate of at least 1 arterial conduit ranging from 88.5% to 97%,⁷ which is lower than the bar of current standard of care set by the surgical community that approaches 100%. It is likely that an even greater outcome advantage with CABG could have been realized with a more frequent use of arterial conduits. Except for the MASS II trial, with a reported MAG rate of 41%,³⁷ the majority of RCTs suffered from a low rate of MAG.

Multiple observational studies have documented that MAG improves survival and freedom from reinterventions.^{34,35} The seminal study by Lytle and colleagues³⁴ showed that 2 ITAs are better than 1, with decreased risk of deaths and reinterventions. The presence of DM was an incremental risk factor for worse outcomes. In the diabetic subpopulation, 11% received 2 ITA grafts compared with 13% in the nondiabetic patients, with a significant survival advantage when BITA was deployed as a surgical strategy.³⁴ Chikwe and colleagues³⁵ found that MAG was associated with decreased mortality and lower risk of myocardial infarctions and reinterventions in a large statewide registry, in which DM was present in 40% of patients. Furthermore, a large population-based study from British Columbia demonstrated a consistent benefit of MAG among diabetic patients, with a greater absolute mortality rate reduction at 15 years among diabetic patients compared with nondiabetic patients (9.55% vs 3.8%).¹³

Puskas and colleagues¹⁴ noted that BITA grafting conferred a 35% mortality reduction at 8 years compared with single ITA use among patients with DM and MVD.¹⁴ In addition, in a 30-year follow-up study of propensity-matched cohorts, BITA grafting significantly enhanced survival with a median gain of 3.3 years and without increasing perioperative morbidity.¹⁵

RA use is also associated with a significant late survival advantage compared with saphenous vein graft use in diabetic patients¹² and compares favorably with right ITA use.³⁰ In general, regardless of whether a second ITA or an RA is used to supplement the left ITA to LAD, it is best to maximize the amount of myocardium supplied by the arterial grafts by using them in bypassing anatomically important targets. Such a strategy is associated with an incremental survival advantage.⁴¹

Multiple barriers have been implicated in the lack of widespread adoption of MAG, especially BITA use, but

perhaps the most cited in diabetic patients is the concern for wound healing.⁴² ITA skeletonization has significantly reduced sternal wound complications and has become routine practice for many MAG surgeons. Skeletonization causes less disruption to sternal collateral blood flow by less cautery use and by dividing ITA branches closer to their origins. The increased risk of wound infections and other sternal complications, initially seen with BITA harvesting, can be mitigated with the adoption of the skeletonization technique even in patients with DM.⁴³

The following points can be inferred regarding DM and CAD:

1. DM is on the rise and is strongly associated with diffuse MVD.
2. CAD is a major cause of death in diabetic patients.
3. DM is an independent risk factor for late cardiovascular mortality and is a marker for worse short- and long-term outcomes after percutaneous and surgical revascularization.
4. Compared with PCI, CABG provides more complete revascularization and can offer protection against future lesions regardless of the complexity of the coronary disease. The clinical translation is improved survival and freedom from MACCE observed with CABG.
5. MAG use is strongly encouraged because it can provide additional outcome advantage (including survival benefit) in diabetic patients with MVD undergoing surgical revascularization.
6. ITA skeletonization decreases wound complications in BITA CABG.

CONCLUSIONS

The risk of premature morbidity and mortality is increased in diabetic patients, with cardiovascular disease being the leading cause of death. A consistent finding among most studies is that diabetic patients with MVD benefit more from CABG compared with PCI. The long-term advantage of CABG can be enhanced with the judicious use of MAG strategies.

Conflict of Interest Statement

Disclosures: The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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