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REVIEW

Coronary artery bypass graft (CABG) and the diabetic patient: current perspectives

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Abstract: Diabetes increases both the severity and the risks of coronary artery disease. For such patients, revascularization by coronary artery bypass grafting (CABG) has consistently improved survival and event free survival in multiple studies compared to percutaneous revascularization (PCI). Evolving treatments, the growing volume of patients with diabetes who have coronary disease, and the cost of their care mandates regular reevaluation of the evidence on which treatment by CABG or PCI is based. This review provides current perspectives on the role of CABG based on analysis of information from newly reported major trials such as Taxus drug eluting stent versus coronary artery bypass surgery (SYNTAX) and Future revascularization evaluation in patients with diabetes mellitus:optimal management of multiple vessel disease (FREEDOM). Also evaluated are technical advances in CABG and improvements in the care of CABG patients with diabetes which should be incorporated in "best practice" surgical revascularization. The accumulated evidence shows clear superiority of CABG for patients with diabetes and multivessel disease, and in particular the benefits of CABG employing multiple arterial conduits.

Keywords: Diabetes mellitus, coronary atherosclerosis, revascularization, coronary stent

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Introduction

Diabetes mellitus (DM) is a global epidemic with staggering costs to patients and society. In the US in 2012, 22.3 million people were believed to be living with DM and their medical care and indirect expenses were estimated to cost US$245 billion. Over just 5 years (2007–2012), the prevalence of DM had increased an astonishing 28% while costs ballooned in the same time frame 41%.[1]

Abnormal glucose and insulin levels each subject vascular tissues to conditions that inflict potent injury and impede repair. Clinically, coronary atherosclerosis is worse in every measurable way in patients with DM as manifested by early and more diffuse atherosclerosis producing a greater disease burden, more frequent left main coronary stenosis and multivessel disease, more total occlusions, and an impaired ability to develop collateral circulation.[2,3] The net clinical effect more than doubles the risk of coronary artery disease (CAD) in patients with DM, and the disease is lethal: ischemic CAD causes three quarters of DM-related deaths.[4] In general, revascularization for coronary disease is advised for patients with symptoms unresponsive to optimal medical therapy or to improve the prognosis of patients who have a specific anatomic distribution of disease known to be associated with a substantial burden of ischemia and a high risk of death. Selecting the optimal myocardial revascularization strategy for patients with DM is crucial for patients and for society. This review presents current evidence-based perspectives on revascularization options for patients with DM.

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Percutaneous intervention (PCI) pioneered by Gruentzig[5] promised a less invasive approach to revascularization, but early clinical trials showed surgical revascularization (coronary artery bypass graft [CABG]) yielded better outcomes for patients with DM.[6] PCI and CABG uncovered the unique biology of diabetic vascular disease and patients with DM continued to face worse outcomes, mortality, and complications than similar patients without DM.[7,8] Fundamentally, restenosis is a classic response to mechanical injury of the vessel wall. Endothelial damage causes local thrombosis; superficial and then deep inflammation, which trigger smooth muscle cell proliferation;[9,10] and eventually matrix remodeling and extracellular matrix deposition. Each of these events can be exacerbated by hyperglycemia, hyperinsulinemia, insulin,[11,12] or DM.[13]

PCI versus CABG trials

The Bypass Angioplasty Revascularization Investigation (BARI) trial[6] compared patients who were randomly assigned to treatment of multivessel CAD with percutaneous transluminal coronary angioplasty (PTCA) (without stent) or CABG. Results showed superiority for CABG over balloon angioplasty (PTCA) and a very high rate of reintervention (target vessel revascularization [TVR]) after PTCA (76.8% versus 20.3%, $P<0.001$). Specifically for patients with DM, survival was significantly better after CABG (57.8% versus PTCA 45.5%, $P=0.025$).[7] The BARI results prompted a National Heart, Lung, and Blood Institute alert recommending that patients with DM and multivessel disease undergo CABG as the preferred mode of revascularization. This alert and the subsequent publication of the BARI study did not change clinical practice appreciably. Evidence-based practice was not then a widespread concept. More recently, major professional societies have collaborated to compile comprehensive, evidence-based guidelines for management of CAD, including patients with DM and their specific issues.[14] Unfortunately, compliance with such guidelines has been shown to be poor. For example, in New York State, which has a mandatory audited reporting system, when testing the application of guidelines (from American College of Cardiology [ACC]/American Heart Association [AHA]) from 2005–2007, of those with indications for CABG, only 53% were recommended CABG (and 34% PCI), but where there were indications for PCI, 94% were recommended PCI. Where equipoise existed for CABG and PCI treatments, 93% were recommended PCI and only 5% CABG.[15] More recently, in Europe, despite recommendations by both cardiology and cardiac surgical societies and widespread publicity, a significant number of patients in a single-center study were not receiving optimal treatment according to guidelines.[16] Ideally the patient should be evaluated by a "Heart Team",[14] which can recommend to each patient treatment that is firmly grounded in evidence-based practice, but tailored specifically for the individual. Implicit in this process is an estimation of the risks and benefits of each option: medical, surgical, and interventional.

A concerted attack on the scourge of coronary disease was launched, driven by medical innovation and ingenuity and underpinned by a burgeoning "medical device industrial complex". A cascade of new techniques in response to clinical failures and perceived needs followed. "Plain old balloon angioplasty" was succeeded serially by coronary atherectomy, rotational atherectomy, radiation, bare metal stents (BMS), and generations of drug eluting stents (DES) and dissolvable stents along with new drugs (to modify clotting; eg, glycoprotein IIb/IIIa inhibitors, oral antiplatelet agents, and also antineoplastic agents to modify arterial wall healing after stent placement). These putative improvements were introduced for PCI, adopted enthusiastically in clinical practice, and widely deployed in diabetic patients. BMS were introduced first to combat troublesome restenosis with plain balloon angioplasty, and while BMS were successful in this, mortality was not reduced. Hlatky et al[17] analyzed ten randomized controlled trials comparing CABG with BMS including 1,233 patients with DM (CABG n=615; PCI n=618.) Mortality was substantially lower for CABG versus PCI (hazard ratio [HR] 0.70, 0.56–0.87) and at 8 years mortality (22% versus 34%) significantly favored CABG. DES followed. DES with sirolimus[18] and paclitaxel[19] each reduced angiographic restenosis for patients with DM and transformed restenosis from a diffuse to a focal pattern. However, DM remained an independent predictor of TVR (odds ratio [OR] 1.65, $P=0.0351$), while in those treated with insulin, the angiographic restenosis rate was doubled. For patients with DM, the number needed to treat with DES to avoid one additional restenosis per year compared with BMS ranged from 21 to 47 in patients treated with one stent and 11 to 27 in patients with multiple stents.[20] DM remained an independent predictor of overall, early, and late stent thrombosis.[21,22]

The most complex patients with DM (eg, those with multivessel and diffuse disease and impaired left ventricular function) were generally excluded from enrollment in the DES trials and in real world practice, the benefits of stents in patients with DM are less impressive. Despite reducing restenosis and TVR, the hard end points of death or myocardial infarction (MI) were not reduced by DES in the Swedish Coronary Angiography and Angioplasty Registry.[20] Multiple studies have been published comparing DES with CABG, and usually show CABG to be superior.[23] The large, mandatory New York State Registry strongly supports the benefit of CABG over DES at 18 months for mortality, and for the composite of death/MI for patients with triple or double vessel disease.[24] CABG also had lower rates of TVR than PCI. Patients with DM usually have extensive CAD and require multiple grafts. Incomplete revascularization (by DES) was associated with higher 18-month mortality (HR: 1.23) and MI.[25]

The unique database collaboration, the ASCERT™ (American College of Cardiology Foundation-The Society of Thoracic Surgeons Collaboration on the Comparative Effectiveness of Revascularization sTrategies) study compared outcomes of PCI versus CABG, correlated with follow-up data from the Centers for Medicare and Medicaid Services (CMS).[26] Of 190,000 patients (between 2004–2007), more than one third were diabetic, while 10% in each arm were on insulin. PCI used DES (80%), BMS (14%), and no stent for only 6% (PTCA only). There was a clear survival benefit for CABG: mortality was 20% lower at 4 years. The CABG advantage persisted across all subgroups analyzed (sex, age, body mass index, chronic lung disease, left ventricular function, renal function, and the presence or absence of DM).

Three studies were performed in the Veteran Administration system in the United States. Angina with extremely serious operative mortality evaluation (AWESOME)[27] reported no significant difference in mortality at 5 years in patients randomized to PCI or CABG. This study enrolled only patients with unstable angina who were considered to be at high risk for surgery; however, only 144 diabetic patients were randomized and 39% of those treated with CABG were reoperations, so valid comparisons cannot be made. Importantly, despite the selection of "high risk" patients, the results of CABG were quite good (mortality 5%, stroke 1%, and renal failure 2%), but the use of arterial grafts was low by contemporary standards. The Veterans Affairs Coronary Artery Revascularization in Diabetes Study (VA CARDS)[28] enrolled patients with DM who had single-vessel proximal left anterior descending artery (LAD) or multivessel disease and randomized them to revascularization with CABG or PCI with DES. A composite primary outcome (nonfatal MI or death) at 2 years was the specified end point. Unfortunately, recruitment was slow and the study was stopped having enrolled just 25% of the intended sample and therefore was severely underpowered. Treatment with CABG was still better (HR: 0.89) Most significantly, all cause mortality was quadruple at 2 years in PCI patients (5.0% CABG versus 21% PCI; HR: 0.30; 95% confidence interval [CI]: 0.11–0.80) and nonfatal MI was triple for PCI (6.2% CABG versus 15% PCI; HR: 3.32; 95% CI: 1.07–10.30). The Coronary Artery Revascularization in Diabetes (CARDIA)[29] study randomized 510 patients, all with DM (2002–2007) with proximal LAD or multivessel disease to treatment by CABG or PCI with DES (sirolimus) 71% or BMS (29%). The primary end point specified a composite of death, MI, or stroke. At 1 year the composite end point was not different, but mortality approached statistical significance, while MI and TVR were significantly less common after CABG. PCI outcome was clearly worse at 1 year for insulin-dependent patients.

The SYNTAX study (Synergy between PCI with Taxus and Cardiac Surgery)[30,31] was a seminal multicenter randomized trial of three-vessel or left main coronary disease treated by DES or CABG. SYNTAX established a new standardized score to compare the distribution and severity of CAD. At 4 years, all cause and cardiac mortality were each lower after CABG, mainly in patients in the moderate or high SYNTAX score tertiles.

SYNTAX prespecified a DM subgroup.[30,31] Among this cohort (n=452), PCI patients had significantly more cardiac deaths at 5 years than CABG (12.7% versus 6.5%, respectively, $P=0.034$). TVR was also higher among patients with DM after PCI than after CABG (35.3% versus 14.6%, respectively, $P<0.001$). The stroke rate for CABG was 4.7% at 5 years, not significantly different than the PCI stroke rate of 3.0% ($P=0.34$). The interval stroke rates year to year were not different after the first year. After PCI, MI was significantly more common for patients without DM (HR 2.90), but for patients with DM, although the HR for MI was high (HR 1.62), the CIs were very wide. (0.77–3.41).[31] More TVR ensured that major adverse cardiac and cerebrovascular event (MACCE) rates were higher for PCI at 1, 3, and 5 years than for CABG (at 5 years: 46.5% versus 29.0%, respectively; $P<0.001$). The primary composite outcome (any cause death/MI/stroke) was significantly different too (26.6% PCI versus 18.7% CABG, $P=0.005$).[30] The difference in MACCE rates between PCI and CABG was wider for patients with DM than for those without DM.

Importantly, insulin-treated patients fared poorly with PCI: their MACCE rate was doubled compared with CABG and mortality almost tripled (12.6% versus 4.5%, respectively; $P \leq 0.06$) For patients with DM but not on insulin, differences were more modest.[30]

The subgroup of SYNTAX patients with left main stenosis have been evaluated (although statistically such inferences are hypothesis generating only). With fewer strokes and relatively less frequent need for TVR (compared with the overall PCI cohort), the primary end point was not different between PCI and CABG treatments for the left main cohort, suggesting that PCI for such patients might be an alternative to CABG.[30] The statistical validity of this approach will need to be proven and information accrued about the durability of left main stents.

Specifically for the patients in the high SYNTAX score cohort, mortality was significantly lower for CABG-treated patients than for PCI (4.1% versus 13.5%, respectively; $P \leq 0.04$).[30] However, in diabetic patients even in the low SYNTAX score tertile, there was a significantly higher event rate after PCI than after CABG (39.4% versus 17.2%, respectively; $P=0.006$).[30] In SYNTAX, the final multivariate model found that DM was independently predictive for PCI patients of MACCE and TVR.[30] CABG neutralized the effect of DM, so outcomes after CABG were not different for DM patients or those without DM. SYNTAX scores did not predict stroke or MI. SYNTAX score correlated with outcomes after PCI, but not after CABG: it is thought that in the CABG patients, the more distal location of bypass grafts negates the impact of new or progressive atherosclerotic disease or plaque rupture in segments of grafted coronary arteries proximal to the anastomotic sites.

The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial[32] was specifically designed to identify the optimal revascularization strategy for patients with DM and multivessel CAD. Enrolled were patients with DM who had double (17%) or triple vessel disease (83%) but without left main stenosis. Between 2005–2010, 33,000 patients were screened; 3,300 were eligible and 1,900 consented and were randomized to revascularization with CABG or PCI (DES 94%). The primary outcome was a composite of all cause death, nonfatal MI, and nonfatal stroke. Mean age was 63.1±9.1 years and mean hemoglobin A_{1C} as an index of blood sugar control was 7.8%. Most patients had normal left ventricular function (mean ejection fraction 66%) and median follow-up was 3.8 years. The mean SYNTAX score was 26.2±8.6 (middle tertile) and the SYNTAX score did not predict outcomes after CABG, but did predict worse outcomes after PCI.

At 30 days, the primary outcome favored PCI patients, but at all points after 30 days, the primary outcome favored CABG (PCI 26.6% versus CABG 18.7%; $P=0.005$), and the relative risk (RR) reduction was 30% for CABG. Results were mainly driven by differences between PCI and CABG in MI (13.9% versus 6.0%, respectively; $P<0.001$) and death from any cause (16.3% versus 10.9%, respectively; $P<0.049$).[32]

On follow-up, only a quarter of patients were beyond 4 years from treatment, but 5-year all-cause mortality was worse after PCI. Patients suffered more MI after PCI and the MACCE rates at 1 year significantly favored CABG (CABG 11.8% versus PCI 16.8%; $P=0.004$), largely from TVR. The benefit of CABG versus PCI was consistent across all prespecified subgroups.[32]

In FREEDOM patients with DM and significant CAD, CABG was unequivocally superior to PCI in reducing late MI and death. The findings confirm other studies of patients with DM and multivessel CAD, which, since BARI, have consistently reported worse outcomes after PCI when compared with CABG.

Stroke is likely the most feared complication of CABG. The stroke rate in FREEDOM was not statistically different at 1 year, but was higher for CABG than PCI at 5 years (5.2% versus 2.4%, respectively; $P=0.03$). The greatest risk of stroke for CABG (which included preoperative strokes in the intent-to-treat analysis) occurred in the first 30 days, rose slower than in PCI for the remainder of the first year, equally with PCI in the second year, and then rose disproportionately (from 2.7% at 2 years to 5.2% at 5 years) compared with PCI patients (for whom the stroke rate increased from 1.5% at 2 years to 2.4% at 5 years). No explanation has been advanced to account for the excess strokes late after CABG in FREEDOM, which is at odds with SYNTAX[31] and other trials. There is no clear causal link between stroke and surgery performed 2–5 years prior; this apparent discrepancy will need to be investigated further. Clinically, thoughtful evaluation of each patient's perioperative and long-term risks of stroke is important, and the choice between PCI and surgery must take into account peripheral vascular disease, old or recent strokes, carotid artery stenosis, and calcification of the ascending aorta. Patients with a high risk of stroke may prefer to have PCI and accept the higher risk of MI or death. Surgical strategies to reduce stroke risk include off-pump coronary artery bypass (OPCAB) surgery; intraoperative epiaortic scanning with ultrasound; and "no touch" coronary bypass with graft inflow based solely on one or both internal thoracic arteries (ITAs).

Some have suggested that newer stents than those used in FREEDOM could improve PCI outcome. This contention is not supported by studies comparing newer against older stents, which show only limited improvement in outcomes[33] – improvement not important enough to undermine the conclusions of FREEDOM.

Cost-effectiveness comparisons were evaluated in FREEDOM using several models to calculate the life-years added by CABG. Calculated cost ranged from US$8,100 to US$27,000 per quality-adjusted life-year added, all below the common US$50,000 benchmark. CABG for diabetic patients with multivessel CAD saved an additional five lives for every 100 patients treated at an additional cost versus PCI over 5 years of just US$3,600 per patient.[34]

Implications of the FREEDOM trial

An editorial by Hlatky (a cardiologist) in the New England Journal of Medicine stated:

> "Mortality has been consistently reduced by CABG, as compared with PCI, in more than 4,000 patients with DM who have been evaluated in 13 clinical trials. The controversy should finally be settled."[35]

A useful summary of PCI versus CABG trials in DM has been published.[36]

What makes CABG outcomes superior to PCI?

Although all trials have not confirmed a uniform survival advantage for CABG, this is commonly explained by trial designs which enrolled highly selected and low risk populations, differing from patients in clinical practice.[37] Pathologically, most coronary disease is located in the proximal portions of epicardial arteries, while DM does not seem to affect the patency of internal mammary grafts.[38,39] Bypasses to the mid-coronary vessel, where grafts are usually anastomosed, treat the proximal culprit lesion and also prevent against new disease, progression of stenosis, or plaque rupture, which can develop in the native vessel proximal to a patent graft insertion. Surgical revascularization by CABG is also usually more complete. For CABG patients, only new disease within the graft (uncommon in arterial conduits) or in the native artery beyond the graft is important. PCI can treat proximal CAD effectively, but the long-term benefits of PCI are compromised by new disease in the native vessels proximal or distal to the stent, as well as by disease within the stented segment (the one place where DES have been less vulnerable). Therefore, the SYNTAX score, based as it is on the extent of proximal obstructions, does not predict outcomes of CABG, but is definitely predictive for PCI outcomes. So new generations of stents have reduced rates of restenosis, but consistently fail to reduce MI rates or mortality.

Further improving the results of CABG

CABG has been established as the most effective revascularization therapy option for patients with DM, yet when compared to patients who do not have DM, outcomes after CABG remain inferior (higher operative and 30-day mortality, more frequent major postoperative complications, stroke, renal failure, and sternal wound infection). Patients with DM have more frequent comorbidities (obesity, hypertension, renal insufficiency, peripheral vascular disease, and cerebrovascular disease), but the burden of comorbidities accounts for only part of the poorer outcomes for patients with DM. Elevated hemoglobin A_{1c} was associated with worse outcomes after CABG and with reduced long-term survival.[40,41] Long-term survival after CABG in patients with DM is also reduced compared with similar patients who do not have DM: this is due to more frequent comorbidities, and the predisposition to more rapid progression of atherosclerosis in native vessels and in their vein grafts with reduced long-term patency of saphenous vein grafts (SVGs).[42] Better initial operation, careful control of blood sugar perioperatively and improved long-term medical management and supervision of the patients, education, and compliance all play an important role, and a multiarterial graft strategy is likely ideal to minimizing complications and setting up long-term graft patency and patient survival.

Risk scoring for CABG

Data from the mandatory New York State Cardiac Reporting System were used to construct a risk prediction tool for in-hospital mortality.[43] Multivariable analysis based on 2002 data generated ten risk factors, but DM was not significant. The 30-day mortality score was updated in 2013, now with only seven risk factors (age, hemodynamic state, ejection fraction, renal failure, body mass index, congestive heart failure, and now including DM).[44] The streamlined 2013 scoring system was tested and validated in five western states. Unfortunately none of the risk factors can be meaningfully modified in the time frame before

CABG. A risk score for predicting long-term mortality was also developed: significant predictors of long-term death included DM.[45]

Other widely used systems exist to help calculate the risk of CABG. Implicit in the "Heart Team" approach to the patient with CAD is analysis of the relative benefits and risks of the proposed procedure for the specific patient, estimated from an established risk calculator and adjusted for local factors.

OPCAB versus ONCAB (off-pump versus on-pump CABG)

In the most recent New York State database report (2010), 25% of CABGs are done off-pump (OPCAB). Concerns about the completeness of revascularization and no reproducible reduction in complication rates have reduced enthusiasm for OPCAB, but 3-year mortality was not different on- or off-pump, although OPCAB did have higher TVR (HR 1.55).[46] In one report, patients with DM did just as well as patients without DM at 5 years after total arterial OPCAB for multivessel coronary disease (by angiographic results, long-term survival, and clinical events).[47]

Effect of PCI prior to CABG

A strategy advocating PCI first, relying on later CABG has been shown to be flawed in multiple studies in Europe and the US:[48,49] operative risks increase and short-term and long-term survival are worse where CABG is performed after PCI. Prior PCI is an independent risk factor for CABG. A microsimulation study estimated that PCI prior to CABG worsened 10-year survival by 3.3%.[50]

Fractional flow reserve (FFR)

The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study of angioplasty for multivessel PCI showed improved graft patency when stents were placed only for coronary lesions with objective confirmation of flow restriction compared with visual assessment of stenosis.[51] Wider application of this technique to determine hemodynamically significant stenoses could improve outcomes for CABG by limiting the competitive flow, which might promote early graft closure.[52] FFR is, however, based on assumption of a normal microcirculation and in the distal small vessel disease prevalent in patients with DM, FFR may not accurately reflect flow beyond the tip of the catheter. The use of FFR to guide grafting of lesions with a visual stenosis 50%–70% will need to be defined in prospective randomized trials with longer clinical follow-up.[53]

Multiple arterial graft strategy

SVGs have been shown to fail at a greater rate in patients with DM, yet left ITA (LITA) patency remains excellent in multiple large series.[38,54] SVG endothelial and media hyperplasia diminish patency. Careful harvesting, avoiding trauma and over-distension, and preserving vasa vasora may enhance long-term patency, as may the use of statins.[54] The disparity in patency rates of ITA and saphenous veins triggered evaluation of other arterial conduits. The right ITA (RITA) offers the advantage of structure and biochemical function identical to the LITA, but RITA deployment is limited by the restricted reach of the pedicled RITA and risk of sternal devascularization from bilateral ITA (BITA) harvest. In a diabetic population, the morbidity and mortality risks of deep sternal wound infection (DSWI) are an important consideration, and the relative weight of increased early risk versus possible late survival advantage might explain why RITA was uncommon (STS 6% in all-comers and likely far lower in patients with DM). The decision by CMS to label DSWI a "never event" and refuse reimbursement for the costs of this complication will likely reinforce the trend away from BITA use. Techniques for skeletonized harvest extend the reach of the pedicled RITA, and Tatoulis et al have shown clearly that patency of pedicled and free RITA are indistinguishable and excellent.[54] In Dorman et al's large series[55] of patients with DM, although DSWI was increased, BITA use was not a risk factor for DSWI. Similar data were reported from Emory University,[56] where DM had doubled the risk of DSWI but BITA was not a risk factor for DSWI. In aggregate, it seems that BITA can be used in patients with DM, but the rate of sternal wound complications is always higher than if only the LITA is harvested. Although skeletonized harvest is likely an important factor in limiting the difference in DSWI for BITA, obesity and female sex represent additional factors that might argue against BITA harvest.

The radial artery (RA) graft was reintroduced by Acar et al[57] and offers the advantages of usable length, and a caliber that is well matched to coronary vessels and convenient for direct aortic anastomosis for inflow. With familiarity, bilateral harvest has become more frequent, allowing, in combination with LITA, multiple arterial grafts and total arterial revascularization. The RA is a medium-sized thick-walled vessel and prone to spasm. Among Acar et al's important discoveries was the importance of atraumatic harvest of the RA and avoiding hydrostatic dilatation by the use of pharmacologic vasodilation instead. With these principles and use of systemic antispasm therapy with calcium channel blockers or nitrates, multiple series from around the world have reported excellent results (in terms of patient survival and graft patency). Importantly, RA graft has been shown to be superior to SVG in women,[58] in older patients,[59] in primary CABG,[60] and in reoperative CABG.[61]

Two commonly quoted exceptions to the trend of excellent RA graft results are papers by Khot et al[62] and Ruttman et al.[63] Khot et al[62] reported 310 symptomatic patients from the early experience of the Cleveland clinic. RA graft patency was worse than patency of SVG, the first study to yield this finding. However, 25% of their patients also had RITA grafts and 22% were reoperations. RA sequential grafts were constructed in 42%. Of their patients, 15% had their RA harvested and used at institutions other than the Cleveland Clinic. Important details of the degree of stenosis and graft deployment, harvest, and intraoperative management were not forthcoming and likely explain the extraordinarily low RA patency (51% at 18 months). Ruttman et al[63] conducted a propensity-matched comparison of RITA versus RA grafts: patient survival at 33 months was far better for RITA patients, and like Khot et al (but unlike all other series) RA graft patency was strikingly worse than ITA graft and even SVG patency (RA 62% versus SVG 79%). RA patients suffered almost ten-fold increases in stroke and postoperative MI. Reoperations for bleeding (6.5%) and sternal dehiscence (3.6%) were unusually high in RA patients. DM patients constituted 21% of BITA patients and 25% of RA patients. Emergency reoperation for acute RA graft failure during the postoperative period for RA, an extraordinary event, was required in 1% of their RA patients. Follow-up was twice as long for RA patients. Use of a partial occlusion clamp in 95% of RA cases likely explains the stroke difference, especially since 24% of RITA patients had no aortic anastomosis. A clue to the likely explanation for the unusually poor outcomes in this series can be found in the author's reply to a letter to the editor,[64] which mentions "moderate supraphysiologic dilatation of the RA graft after harvesting was performed in all cases". This was clearly a harmful method that violated Acar et al's[57] clear and evidence-based recommendations. Our experience[60] and the large protocol-driven angiographic series by Tatoulis et al and reports from Collins et al[65] and Possati et al[66] prove that excellent long-term RA patency is an achievable norm. Strict attention to the principles elaborated by Acar et al is necessary to achieve optimal results. We[67] have compared outcomes in RITA and RA patients with DM in a propensity-matched study and found comparable late survival (RA 80% and RITA 74% at 10 years). Unsurprisingly the rates of respiratory failure and DSWI were greater for RITA patients. This contradicts the findings of Navia et al,[68] but it appears their study was biased by the effect of the OPCAB learning curve on the RA cohort. Locker et al[69] reported from the Mayo Clinic the clear benefit of multiple arterial grafts on late survival.

We[70] and Zacharias et al[71] reported a strong survival benefit of RA grafts compared to SVGs, specifically in patients with DM. The RA is an attractive alternative arterial conduit to the RITA graft, achieving for patients with DM the survival benefit of arterial grafting without the added risk of DSWI. The aggregate data suggest that RITA graft may offer slightly superior patency to RA, but these series are affected by selection bias and use of the RA to a target vessel only after the LITA and RITA have been chosen to bypass the LAD and then the second best target vessel (most often in the circumflex distribution, though a few surgeons have used RITA–LAD, a strategy that possesses great hazard for subsequent reoperation sternotomy; eg, for aortic valve replacement). The RA certainly avoids the incremental risk that BITA creates for DSWI. We await the outcomes of the prospective randomized trial from Taggart et al arterial revascularization trial [ART], which should provide the clearest possible evidence of any difference between RA and RITA for arterial grafting.

If two arterial grafts are superior, might even more be better still? Testing this strategy showed a trend toward survival benefit for patients with DM (RR 0.77; but 95% CI: 0.56–1.07) and very clear benefit for patients without DM (RR 0.50; 95% CI: 0.37–0.69). Completeness of revascularization emerged as an important long-term determinant of survival.[72]

Enthusiasm for the right gastroepiloic artery (GEPA) as a conduit is limited to a few centers, but multiple reports confirm the safety of this technique and good late survival rates. Concerns remain about a tendency to spasm in the pedicled GEPA.[73,74] Spasm of arterial conduit is commonest perioperatively, but can occur weeks or months later. Complete occlusion occurs early from technical error. Localized stenosis may occur from damage at harvest. "String sign", a patent, but ineffectual graft, is the result of competitive flow. LITA grafts are said to be able to adapt and "reopen" later if the native vessel proximal to the anastomosis stenoses. SVGs are unaffected by competitive flow irrespective of the degree of stenosis of the target artery over the range of 50%–100%. All arterial grafts are affected by competitive flow, but ITAs are least affected, while RA and GEPA are most vulnerable to competitive flow if the native target vessel stenosis is below 60%. It is usually agreed that a 1 mm diameter of the stenosed native vessel is the threshold for significant influence on arterial graft patency.[75]

Current ACC guidelines[14] for revascularization of multivessel disease, which describe DM as an important factor when deciding on a strategy, are likely to be strengthened in their next iteration. On the basis of the current body of evidence, CABG should be preferred over PCI in patients with DM and multivessel disease with complex anatomy exemplified by SYNTAX scores >22, and even in all patients with DM with multivessel disease. FREEDOM results are clear and support wide indications for CABG for patients with multivessel disease, where CABG improves survival over PCI and consistently lowers combined rates of death or MI and TVR. The complementary results of SYNTAX and FREEDOM are likely to endure because CABG and PCI achieve their benefits in quite different ways.

Summary for CABG in diabetic patients

- CABG is superior in terms of survival, recurrent MI, and freedom from TVR for patients with DM with moderate to severe symptoms and CAD with either significant proximal LAD involvement, or left main stenosis ≥50%.
- Multiple arterial grafts (LITA plus either RITA or RA) improve survival.
- RA or RITA grafts produce equivalent survival benefit.
- RA grafts generate fewer major adverse events than RITA grafts.
- The RA is ideal for the multiple arterial graft strategy in diabetic patients.
- For patients with DM with normal left ventricular function who have single-vessel or double-vessel disease (not involving the proximal LAD), there is little prognostic benefit from any intervention over optimum medical therapy.[76] In such patients who require intervention for failed medical therapy, there is no survival advantage between PCI or CABG, but PCI has a significantly higher risk of TVR. While DES did reduce restenosis compared with BMS in patients with DM, DES still have consistently higher TVR rates compared with CABG.[34,77]

Important aspects of postoperative care: glucose control

Hyperglycemia prior to, during or immediately after CABG predicts increased perioperative morbidity and mortality in patients with (and without) DM. Hospital length of stay and long-term survival are impacted. An excellent executive summary from the STS[78] set out guidelines for perioperative management. Important recommendations are summarized below:

- Glycemic control (<180 mg/dL) is best achieved with continuous insulin infusions, but extremely tight control (<140 mg/dL) is not recommended.
- All patients with DM undergoing cardiac surgery must be on an insulin infusion in the operating room, and for at least 24 hours postoperatively to maintain serum glucose ≤180 mg/dL (evidence level B).[79] Prior to surgery, it is reasonable to maintain blood glucose concentration ≤180 mg/dL (evidence level B).
- Any patient with (or without) DM who has persistently elevated serum glucose >180 mg/dL should receive intravenous insulin infusions to maintain serum glucose <180 mg/dL for the duration of their intensive care unit care (evidence level A). Before insulin infusions are discontinued, patients should be transitioned to subcutaneous insulin using institutional protocols (evidence level B).

There is some evidence favoring glucagon-like peptide for perioperative control of blood sugar in diabetic patients.[80] Lower initial blood glucose values, which reflect an impaired stress response immediately after CABG, have been associated with increased mortality, and a significant delay in achieving tight glycemic control with intensive insulin.[81]

After CABG, glucose insulin potassium infusion reduced atrial fibrillation, myocardial injury, wound infection, and hospital stay,[82] but enthusiasm for glucose insulin potassium is limited to a few centers.

Vein graft disease

When SVG disease occurs, PCI is generally preferable to reoperative CABG, but PCI for vein graft disease in patients with DM may be less effective because of more frequent calcific vein graft degeneration.[83] Restenosis in patients with DM is associated pathologically with excess intimal fibrosis and reduced cell content.[84] The best primary operation is protective. Vein graft PCI with DES significantly reduced TVR (versus BMS), but did not provide clear benefits on mortality and MI.[85]

Secondary prevention

Patients with DM benefit from the pleiotropic effects of statins, independent of the low-density lipoprotein cholesterol lowering effects.[86] Aspirin resistance is important in revascularized patients with DM, where more than 20% appear aspirin resistant.[87,88]

In diabetic patients undergoing cardiac rehabilitation, an improvement of the lipid profile has been observed, but hypertension and hyperglycemia are still not optimally addressed. CABG patients were less likely than PCI patients to fill prescriptions for secondary preventive medications (statins, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, or beta blockers) and to use those medications consistently in the first year after the procedure.[89]

Conclusion

- Patients with DM develop worse forms of atherosclerotic CAD and medical management of such coronary disease has consistently yielded results inferior to revascularization.
- Notwithstanding developments in PCI, diabetics still do less well with PCI than patients who do not have DM.
- PCI is established as the appropriate treatment for patients with DM presenting with acute coronary syndromes (non-ST segment elevation MI and ST-elevation MI).
- Diabetic patients benefit from the same medical management and secondary risk modification as patients without DM.
- Level 1 evidence from the SYNTAX trial[30] establishes CABG as the revascularization option of choice in patients with more complex CAD.
- Level 1 evidence from the FREEDOM trial[32] has confirmed that diabetic patients with multivessel CAD benefit from revascularization by CABG.
- Improvements in surgical revascularization benefiting patients with DM include wider use of the RA as a bypass conduit in place of the saphenous vein, and improved perioperative glucose management.

Disclosure

The authors report no conflicts of interest in this work.

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