Coronary intervention in diabetes: is it different

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INTRODUCTION

Diabetics are at an increased risk of cardiovascular morbidity and mortality as a consequence of inherent metabolic abnormalities and comorbidities. Furthermore, these patients derive less benefit from the standard therapies of coronary artery disease (CAD); the unique pathophysiological response to arterial injury has a profound effect on outcomes of percutaneous coronary interventions (PCIs). However, as the technology, techniques and expertise of operators in PCI are evolving, the understanding of revascularisation strategies and patterns of clinical practice are changing. In this review, we discuss specific issues related to cardiac intervention in diabetics.

MAGNITUDE OF THE PROBLEM, PATHOPHYSIOLOGY AND MECHANISTIC INSIGHTS INTO ADVERSE OUTCOMES AFTER REVASCULARISATION

Currently, diabetes affects >180 million people worldwide. In the current era of advanced medical therapy, improved medical facilities and medical infrastructure, the term myocardial infarction (MI) equivalent might not hold true. However, despite improved outcomes, the gradient of increased risk of mortality and morbidity as compared with non-diabetics persists throughout the spectrum of CAD. Diabetics constitute around one quarter of patients undergoing revascularisation. Both types of revascularisation strategies have been evaluated extensively. Preoperative mortality, repeat revascularisation and long-term mortality are the issues of concern.

Diabetes is a metabolic disorder characterised by chronic hyperglycaemia and insulin resistance. Disturbed delicate balance of fibrinolytic system as well as abnormalities of platelet structure and function results (box 1) in a persistent prothrombotic milieu.2 (A) Metabolic factors: Hyperglycaemia include endothelial dysfunction, vascular effects of advanced glycation end products, adverse effects of circulating free fatty acids and increased systemic inflammation. (B) Vascular anatomic characters: Diabetics have more frequent diffuse disease, higher prevalence of extensive CAD, left main disease, multivessel disease and occlusions. The narrow calibrated vessels are associated with impaired collateral development. (C) Adverse prothrombotic milieu and high atherosclerotic burden: Proteofibrinolytic system and platelet biology are unfavourably altered in diabetes and a state of platelet activation exists. Glycoprotein Iib/IIia (GP Iib/IIia) receptor density is high and increased thrombosis is an independent marker of adverse outcomes following PCI. Diabetics have a higher atherosclerotic burden and plaques, which are high risk and vulnerable to rupture.

ADVERSE OUTCOMES AFTER CORONARY INTERVENTION IN DIABETICS

Balloon angioplasty and bare metal stent implantation

Procedure-related and in-hospital mortality

Early studies had shown more procedural complications and in-hospital complications twofold higher in diabetics. However, the rate of angiographic success was same as non-diabetics.3 The complication rates fell in later studies, in-hospital mortality (1.9% vs 4.3%), MI (1.0% vs 7.4%), an in-hospital coronary artery bypass grafting (CABG) surgery (0.8% vs 6.2%).4 Patients with diabetes poorly tolerate the ischemic complications of PCI.5 Renal dysfunction after PCI occurs more frequently in diabetics.6

Repeat revascularisation and long-term outcomes

Initial data from the National Heart, Lung and Blood Institute reported restenosis rates exceeding 47% as compared with non-diabetics.7 An absolute 10% difference exists between patients with and without diabetes regarding repeat revascularisation. The restenotic process more often results in total occlusions, MI and ventricular dysfunction in diabetics than in non-diabetics.8

Drug-eluting stents (DES)

Angiographic and clinical outcomes

DESs altered both rate and type of restenosis compared with bare metal stents (BMSs) in diabetic population. However, the result was still inferior to that of non-diabetics. The TAXUS IV and SIRIUS trials provided enough evidence favouring DESs and showed reduction of target lesion revascularisation and restenosis rates to the tune of 65%9 10 Prevention of RESStenosis with Tranilast and its Outcomes, the largest contemporary restenosis trial till date, showed that compared with non-diabetic patients, patients with diabetes were older, more often had comorbid health problems and had more complex culprit stenoses. But even after adjustment for these differences in baseline characteristics, diabetics still had higher 9-month rate of death (relative risk (RR) 1.87, 95% CI 1.31 to 2.68), target vessel revascularisation (TVR; RR 1.27, 95% CI 1.14 to 1.42), and the composite of death/MI and TVR (RR 1.26, 95% CI 1.13 to 1.40).11 Diabetic status was also predictive of major adverse cardiac and cerebrovascular events (MACCE) and mortality in long term.12 While DESs, compared to BMS are effective in reducing the need for repeat revascularisation but whether this translates into reduction in MI and lesser deaths is not clear.14

DES compared with BMS in diabetes

DESs reduce the rate of angiographic restenosis and need of repeat revascularisation in all patients and
The resolute zotarolimus-eluting stent (ZES) and diabetes mellitus

The resolute ZES is a new-generation DES consisting of a thin-strut cobalt alloy bare metal stent coated with a durable bio-stable polymer and the cell-cycle inhibitor zotarolimus. While DESs have been recommended for PCI in patients with diabetes, no DES prior to the resolute has been specifically indicated by the US Food and Drug Administration for use in this high-risk population based on 1-year target vessel failure (TVF) outcomes for on-label non-complex resolute DM patients against a performance goal derived from a meta-analysis of published literature (which included six trials with Cypher SES and Taxus PES) and pooled data for the endeavour ZES. The composite TVF endpoint included cardiac death, MI and TVR. At 1 year, the rate of TVF for the 878 non-complex diabetic resolute patients was 7.8%, significantly lower than the performance goal of 14.5% (p=0.001). The recent data presented at the American College of Cardiology also report similar results.

Stent thrombosis after DES and disease progression

Insulin requiring diabetes is a strong and independent risk factor for probable and definite stent thrombosis with a risk twofold more than non-diabetics. As discussed above, diabetics have a faster progression of native disease and appearance of new lesions is approximately 30% and attributed primarily to new lesions in the treated vessels.

PERCUTANEOUS REvascularisation COMPARED WITH SURGICAL REvascularisation (MULTIVESSEL PCI VS CABG)

Surgical revascularisation is the recommended strategy in diabetics with multivessel disease, but recent trials have resulted in a changing paradigm for revascularisation strategies. Still, most randomised controlled trials have shown higher rates of repeat revascularisation procedures after PCI and survival advantage for CABG over PCI in patients with diabetes.

Trials with long-term results

The Emory Angioplasty versus Surgery Trial (EAST) compared a strategy of initial percutaneous transluminal coronary angioplasty (PTCA) versus CABG in patients with multivessel coronary heart disease. The 8-year survival was greater in patients with diabetes who underwent CABG (75.5%) compared with those who underwent PTCA (60.1%; p=0.23). Diabetic subjects who underwent PCI had a reduced survival rate (60.1% vs 82.6%; p=0.02). Repeat revascularisation occurred in 25.6% of the CABG-treated patients and in 65.3% of the PTCA-treated patients (p=0.001) over a period of 8 years. Bypass Angioplasty Revascularization Investigation (BARI) investigators recently reported sustained survival benefit of CABG at 10 years, 71.0% for PTCA and 73.5% for CABG. However, treated DM patients randomised to CABG had higher survival than those randomised to PCI (PCI 45.5% vs CABG 57.8%, p=0.025).

Registries with long-term result

In contrast to results of EAST, BARI and CABRI which favoured CABG, the 20-year results of a European registry showed reduced survival rates in surgically treated patients.

CABG versus PCI with BMS

Table 1 summarises major randomised trials of multivessel PCI using stents versus CABG, which included patients with diabetes. A recent meta-analysis included 10 major studies of revascularisation reported that in patients with diabetes (CABG, n=615; PCI, n=618), mortality was substantially lower in the CABG group than in the PCI group (p=0.025).23

CABG versus PCI with DES

The SYNTAX trial was a landmark contemporary trial. In diabetics the 1-year composite MACCE rate was significantly higher after PES treatment compared with CABG treatment (RR 1.83). The RR of repeat revascularisation of PES over CABG was 3.18 in diabetics as compared with 1.94 in non-diabetics. Compared with CABG, diabetics had higher mortality after PES use in highly complex lesions, that is, SYNTAX score >33, (4.1% vs 13.5%). Revascularisation with PES resulted in higher repeat revascularisation for both patients without diabetes.
(5.7% vs 11.1%) and patients with diabetes (6.4% vs 20.3%). The authors concluded that CABG remained the standard of care in patients of diabetes with left main or triple vessel disease. Table 2 summarises other contemporary trials. Arterial Revascularization Therapies Study—Part II27 was a major trial which concluded that PCI using SES was safer and more efficacious than using BMS in both diabetic and non-diabetics and was a valuable alternative to CABG in patients with diabetes as well. FREEDOM was a landmark trial that asserted that CABG scores over PCI with DESs in patients with diabetes (all-cause mortality and MI). CABG was better, regardless of SYNTAX score, number of diseased vessels, ejection fraction, race or sex of the patient.

Revascularisation versus medical therapy
In the BARI 2D trial, the rates of death from any cause did not differ significantly between the revascularisation group and the medical therapy group. Prompt revascularisation significantly reduced major cardiovascular events, as compared with intensive medical therapy, among patients who were selected to undergo CABG largely because of a reduction in MI events. The COURAGE Trial also showed that PCI with optimal medical therapy was no better than optimal medical therapy alone for patients with stable CAD in diabetics and non-diabetics.

**IMPROVING OUTCOMES OF PCI IN DIABETICS**

Management of hyperglycaemia after CABG or PCI in patients with diabetes
It is proposed that the strict control of hyperglycaemia immediate postoperative period may have beneficial effect on myocardial energetic. Indirect support for this concept came from studies in critically ill patients with diabetes. No specific studies are available to address this issue and no trial has shown improved PCI outcome after ST-segment-elevation myocardial infarction with the administration of insulin or glucose insulin potassium.

Antiplatelet agents
GP IIb/IIIa receptor antagonists have assumed an important place and provided improved outcomes after PCI in diabetics. A pooled analysis from three trials (n=1462) investigating the use of the GP IIb/IIIa inhibitor, abciximab with PCI in patients with diabetes showed a 2% absolute mortality reduction (4.5% vs 2.5%, p=0.03) at 1 year.28 In recent meta-analysis of six trials of various GP IIb/IIIa inhibitors in acute coronary syndromes, mortality benefit was greater in patients with diabetes (n=1279) who underwent PCI during the index hospitalisation (4.0% vs 1.2%, p=0.002). Contemporary PCI guidelines recommend GP IIb/IIIa inhibitors in patients with unstable CAD and in elective PCI patients with risk factors, such as diabetes. However, ISAR-SWEET trial did not report significant impact of abciximab on the risk of death and MI in patients with diabetes undergoing PCI, but abciximab reduced the risk of restenosis in patients with diabetes receiving BMS.

**Bioabsorbable stents**
After intense preclinical research, there has been a revolutionary advance that of bioresorbable vascular scaffolds (BVSs), which are designed to provide temporary radial support to the vessel, to facilitate administration of antiproliferative drugs and to promote recovery of the artery’s normal structure and physiological function by gradual removal of the scaffolding through a process of biodegradation. BVSs have several advantages, including physiological recovery of the vessel, reduced stent thrombosis and need for antiplatelet therapy, fewer constraints on future interventions in the vessel and its collaterals and the possibility of using non-invasive diagnostic exams, particularly CT angiography. One-year clinical outcomes of patients with diabetes treated with everolimus-eluting BVS, a pooled analysis of the ABSORB and the SPIRIT trial, patients with diabetes treated with the BVS showed similar rates of device-oriented composite endpoint compared with non-diabetic patients treated with the BVS and patients with diabetes treated with everolimus-eluting metal stents (EESs). There were no differences in the incidence of definite or probable scaffold/stent thrombosis (0.7% for both diabetic and non-diabetic patients with the BVS; 1.0% for patients with diabetes with the BVS vs 1.7% for patients with diabetes and EES in the matched study group).

**PRIMARY PCI IN DIABETICS**
Patients with diabetes more often present with late and with congestive heart failure, after a ST elevation MI. CABG is usually done in cases with mechanical complications or failed PCI. PCI is more effective than fibrinolytic therapy. Studies comparing fibrinolytic therapy with primary angioplasty with or without use of GP IIb/IIIa report better short- and long-term outcomes with primary PCI in diabetics. In a recent study of 6315 patients (14% diabetics), 30-day mortality (9.4% vs 5.9%, p=0.001) was higher in patients with diabetes.29 Mortality was lower after primary PCI compared with fibrinolysis in both patients with diabetes (unadjusted OR, 0.49, 95% CI 0.31 to 0.79, p=0.004) and without diabetes (unadjusted OR 0.69, 95% CI 0.54 to 0.86, p=0.001). Recurrent infarction and stroke were also reduced after primary PCI in both patient
groups. After multivariable analysis, primary PCI was associated with decreased 30-day mortality in patients with and without diabetes, with a point estimate of greater benefit in patients with diabetes. In non-ST MI, patients with acute coronary syndrome, there is no interaction between the effect of myocardial revascularisation and diabetic status. However, an early invasive strategy was associated with improved outcomes; in TACTICS-TIMI 18, the benefit in patients with diabetes was greater than in non-diabetics.

OUTCOMES IN INSULIN REQUIRING VERSUS NON-INSULIN REQUIRING DIABETES

The issue of adverse outcomes in patients with insulin requiring diabetes (IRD) versus those who are non-insulin requiring diabetes is far less than resolved. However, the published data indicate that short-term and mid-term outcomes may be worse in IRD population. In a large, real-world multicenter registry of diabetic population from Italy, the use of DES was associated with a moderate reduction in the 2-year risk of TVR, a benefit that was limited to non-insulin-dependent diabetic patients.

In the TRUE Study which evaluated clinical impact of the Taxus stent in non-insulin-requiring vs insulin-requiring diabetes, the 1-month MACE rate was similar (p=0.4) between the two groups, 3% vs 5%. At 7 months, the MACE rate was significantly (p=0.001) lower in the group of diabetics on oral agents (8.5%) than in insulin-requiring diabetics (25.3%). This difference was constant (p<0.01 for all) across deaths (0% vs 8%), TVR (8.4% vs 20.7%) and TLR (3.1% vs 14.6%), while the rate of MI was similar (5.3% vs 4.8%, p=0.7). Further studies are required to evaluate the long-term effects.

CONTEMPORARY GUIDELINES AND APPROACH TO REVASCULARISATION IN DIABETICS

Contemporary PCI guidelines emphasize the long-term survival benefit of CABG over PCI in diabetes with multivessel disease. However, individual clinician judgment on the revascularisation strategy remains an important decisive factor. Although PCIs with DES have narrowed the gap with surgery, the effectiveness of PCI in CABG-eligible diabetic patients with stable multivessel disease is still not clear. Primary PCI is preferred over CABG in diabetics with multivessel disease. However, individual clinician judgment on the revascularisation approach to choice of revascularisation in diabetics with multivessel CAD.

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### Table 2 Trials comparing drug-eluting stent (DES) with CABG in diabetic subjects

| Trial | Patients | Primary endpoint | Intervention | Results |
|-------|----------|-----------------|--------------|---------|
| ARTS 17 | Diabetic patients treated with SES. Multivessel disease that included treatment of the left anterior descending artery and at least one other significant lesion (50% diameter stenosis) in another major epicardial coronary artery | MACCE | Three-year clinical outcome was compared with that of the historical diabetic and non-diabetic arms of the randomised ARTS-I trial | In patients with diabetes, the incidence of MACCE in ARTS-II was similar to that of both PCI and CABG in ARTS-I. Conversely, the incidence of death, CVA and MI was significantly lower in ARTS-II than in ARTS-I (adjusted OR 0.67, 95% CI 0.27 to 1.65) and was similar to that of ARTS-I CABG. |
| CARDIA 18 | Diabetes. Multivessel CAD (two or more stenotic coronary or one in which PCI suitability is unclear). Consensus between a cardiologist and surgeon that adequate revascularisation can be achieved | Death, non-fatal MI or stroke within 1 year | Optimal PCI includes the use of aspirin, clopidogrel, abciximab and SESs in all patients. Modern CABG: defined as one or more arterial conduit with a LIMA graft for the anterior native vessels and off-pump bypass at the surgical team’s discretion | Composite rate of death, MI and stroke: 10.5% in the CABG group and 13.0% in the PCI group (HR 1.25, p=0.39), all-cause mortality rates: 3.2% and 3.2%. Rates of death, MI, stroke or repeat revascularisation were 11.3% and 19.3% (HR 1.77, p=0.02). CABG when compared with drug-eluting stents (69% of patients), the primary outcome rates were 12.4% and 11.6% (HR 0.93, p=0.82). Could not prove PCI non-inferiority. |
| PRECOMBAT 19 | Inclusion: LMCA stenosis ≥50% (visual estimate); angina or documented ischaemia amenable to both PCI or CABG; lesions outside LMCA amenable to both PCI or CABG. Exclusion: previous PCI (≥12 months); previous LMCA PCI; previous CABG; LVEF ≥20%; NYHA heart failure class III or IV | All-cause mortality, MI and stroke at 2 years | Randomisation CABG vs PCI (30% diabetic) | Primary end point: 36 patients in the PCI group as compared with 24 in the CABG group (cumulative event rate, 12.2% vs 8.1%; hazard ratio with PCI, 1.50; 95% CI 0.90 to 2.52; p=0.12). Ischaemia-driven target-vessel revascularisation: 26 patients in the PCI group as compared with 12 patients in the CABG group (cumulative event rate, 9.0% vs 4.2%; HR, 2.18; 95% CI 1.10 to 4.32; p=0.02) Primary composite end point: PCI 26.6% vs CABG 18.7%, p value=0.005 Death from any cause: PCI 16.3% vs CABG 10.9%, p value=0.049 Myocardial infarction: PCI 13.9% vs CABG 6.0%, p value<0.001 Stroke: PCI 2.4% vs CABG 5.2%, p value=0.03 Cardiovascular death: PCI 10.9% vs CABG 6.8%, p value=0.12 |
| FREEDOM 20 | Diabetes. Multivessel CAD (two or more lesions in major arteries), amenable to either PCI with DES or surgical revascularisation. | All-cause mortality, MI and stroke | Compared multivessel stenting using SESs with CABG superiority trial | |

ARTS, Arterial Revascularization Therapies Study; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary interventions; SES, sirolimus-eluting stent.
CONCLUSION
The expanding diabetic population and burden of CAD-related mortality and morbidity mandates a clear perspective in optimising the management of such patients, especially mode of myocardial revascularisation. This becomes even more important in view of the multiple adverse pathophysiological and anatomic characteristics and unique response to arterial injury which confer a relatively poor prognosis and worse outcome after revascularisation procedures. Several early studies comparing CABG surgery versus balloon-only PCI or BMS in subgroups of patients with diabetes with multivessel CAD demonstrated a survival advantage and less repeat revascularisation procedures with an initial surgical strategy. Recent advances in technique use of DES and progress in medical therapy appears to bridge the gap and have made PCI a viable alternative to CABG. Currently, mortality after PCI is comparable with that after CABG, but the need for subsequent revascularisation is greater after PCI. Thus the revascularisation strategy should be individualised based on patient profile, anatomic characteristics of lesions. In general, it is a good idea to have a Heart Team Approach which involves combined assessments by primary physician, interventional cardiologists and cardiac surgeons, also taking into account the patient preference.

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