Management of Stable Angina in Patients with Type 2 Diabetes Mellitus

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The current prevalence of type 2 diabetes mellitus (T2DM), estimated at 8% of the adult population, is predicted to double over the next 12–15 years (1–4). T2DM trebles the risk of developing coronary artery disease (CAD) and once CAD has developed, the risk of acute coronary syndromes (ACS) and clinical risk associated with a coronary event both double in diabetic patients (5–8).

The widespread prevalence of chronic stable angina is associated with worse health-related quality of life and increased hospitalizations (9). The presence of chronic stable angina in patients with T2DM is compounded by the presence of more extensive coronary atherosclerosis (10–12) with a higher ischemic burden at the time of first investigation. Diagnosis is often delayed as patients with T2DM may have symptomless angina and this can affect prognosis as it is the extent of ischemia that dictates outcomes, not symptoms (13).

Stable Angina in Patients with DM

T2DM is an independent risk factor for atherosclerosis, and CAD remains the main cause of morbidity and mortality in this population (14,15). The clinical presentation of angina in patients with DM is often complicated by the absence of classic symptoms of angina pectoris and patients may present with dyspnea on exertion or with no symptoms at all in the presence of prognostically significant cardiac ischemia. The presence of cardiac ischemia is of more relevance in assessing prognosis than the presence of symptoms (angina or angina equivalent) and this was clearly demonstrated in the BARI 2D study where 5-year mortality showed no difference in patients with DM and ischemia stratified on the basis of symptoms, angina equivalent, or asymptomatic. The presence of ischemia following ACS is a powerful marker of prognosis in patients with or without DM (16,17).

Role of Screening for CAD in DM

Many patients with T2DM have silent myocardial ischemia (SMI) on stress testing (17–59%) and these individuals are at higher risk for future cardiovascular events (18–20).

The high prevalence of coronary disease in the diabetic population provides a strong rationale for early screening and aggressive risk factor modulation. However, early clinical detection of myocardial ischemia is challenging as it frequently presents with atypical features and is often clinically silent (21). These challenges are compounded by legitimate questions about the utility of the resulting data in guiding patient care.

Cardiovascular CT is an effective screening test as a zero calcium score has similar clinical import in both diabetic and nondiabetic populations (22). However, the presence of large amounts of calcium can reduce the specificity of CT angiography due to blooming artifacts generated by calcium deposits (23). Although this may limit the positive predictive value of cardiovascular CT, its negative predictive value remains high. Stress echocardiography (no ionising radiation) and SPECT-MPI (ionising radiation) provide information on wall motion as well as ejection fraction. Stress cardiovascular magnetic resonance (CMR) is a viable alternative (24) for patients without significant contraindications (permanent pacemakers, severe claustrophobia, large body girth), although there exists a theoretical risk of nephrogenic systemic fibrosis following administration of gadolinium contrast agents in patients with severe

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renal impairment (eGFR < 30 mL/m^2), but this risk is reduced with modern preparations.

There is evidence that certain biomarkers could be used for risk prediction of ischemic events in T2DM (25–28) with interleukin-6 and activin A showing an association with cardiovascular events and mortality in T2DM (29). These findings need to be reproduced in larger population sets before being recommended for routine risk prediction.

The current American Diabetic Association (ADA) guidelines, however, counsel against the routine screening of diabetic subjects for coronary disease (30) while the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines suggest that in asymptomatic diabetic subjects over the age of 40, coronary artery calcium (CAC) scoring may be of utility in risk stratification (31,32). The impact of such a strategy on outcomes remains to be tested in a prospective randomized trial. Within the UK, such a use of CAC is not currently recommended (33).

Management of Chronic Stable Angina and Associated Risk Factors

There are no specific trials of antianginal agents in the diabetic population and information derives from subgroup analyses, which is suboptimal as the diabetic phenotypes are ill defined. Managing chronic stable angina in patients with DM follows the same principles as those for patients without diabetes, namely controlling ischemic symptoms and reducing ischemic burden. In addition, lifestyle changes (diet, regular exercise, patient education and revascularization) provide the third important pillar for the optimal management of chronic stable angina in patients with DM.

The increased morbidity and mortality in patients with DM and CAD coupled with the likely presence of more than one risk factor are compelling reasons for a more aggressive approach to secondary prevention in such patients.

Pharmacotherapy for relief of ischemic symptoms

Ischemic symptoms can be controlled with β-blockers, nitrates, and/or calcium-channel blockers which work by decreasing myocardial ischemia through decreasing the major determinants of myocardial oxygen demands and/or by increasing coronary blood flow to the ischemic myocardium. Newer antianginal agents have mechanisms related to modulating myocardial metabolism or by inhibiting ion channels (34).

Drugs effective in providing symptom relief are discussed next.

Nitrates

These drugs provide rapid and effective relief of symptoms through dilatation of epicardial coronary arteries and increasing venous capacitance. The main effect of nitrate is on the preload but its direct effect is more pronounced on afterload in higher doses. This results in a reduction in myocardial oxygen consumption and improves overall exercise capacity. Nitrates react with sulfhydryl groups and enzymes (mitochondrial aldehyde dehydrogenase), to produce S-nitrosothiol and finally nitric oxide (NO), which in turn activates smooth muscle guanyl cyclase to increase the cGMP levels. This results in inhibition of Ca^{+2} entry into muscle cells and relaxation of muscle filaments. Similarly, NO also activates platelets cGMP, which reduces intraplatelet calcium concentrations and partially impairs platelet activation (35). The presence of increased NO also leads to improvement in endothelial function and one can speculate that this may be of particular benefit to patients with DM who are known to have endothelial dysfunction. Improved endothelial function further contributes to vasodilatation and optimizes vascular reactivity (36). Lastly, nitroglycerin redistributes coronary blood flow "steal effect" from normally perfused areas of myocardium to ischemic zones (37).

Tolerance to nitrates may develop within 12–24 hours, and can be avoided through implementation of a nitrate-free period of 8 hours each day. Nitroglycerin can be used prophylactically when angina can be expected, such as activity after a meal, emotional stress, sexual activity, and in colder weather (38).

Nicorandil

Nicorandil is a nicotinamide derivative with a nitrate moiety (39) and has a dual mechanism of action. It increases potassium ion conductance by opening ATP sensitive potassium channels, which in turn activates the enzyme guanylate cyclase. Second, due to its nitrate content it causes smooth muscle relaxation thereby reducing afterload and also lowers preload through

venodilatation and promotes expression of endothelial NO synthase.

In patients with chronic stable angina, nicorandil is associated with improved myocardial function during ischemia (40). Impact of nicorandil in angina (IONA) results in a 17% reduction in hospitalization for chest pain, myocardial infarction (MI), and CAD death.

βBlockers

Stimulation of β adrenergic receptors (a class of G-protein coupled receptors, stimulated by catecholamines and mediated by adenyl cyclase β_1 receptors) increases heart rate, contractility, and conduction velocity. Therefore, specific β_1 antagonists lower heart rate both at rest and exercise, contractility, and blood pressure, thereby reducing myocardial oxygen demand. In addition, due to their negative chronotropic effect, β-blockers prolong diastole, raising coronary artery blood flow and myocardial perfusion.

While evidence for prognostic benefits from the use of β-blockers is present only in post-MI and heart failure patients, data in stable CAD patients are lacking. However, retrospective analysis suggests that these drugs may be beneficial as first-line antianginal therapy in stable CAD patients without contraindications (41). In T2DM, *β*-blockers are effective in improving prognosis following MI by reducing the likelihood of reinfarction, sudden death, and ventricular arrhythmias (42,43).

Although some β-blockers may have negative metabolic effects through increasing insulin resistance and masking hypoglycemic symptoms, overall the positive effects of *β*-blockade on prognosis outweigh the negative glucometabolic effects. There appears to be a difference between nonvasodilating agents (e.g., metoprolol and atenolol) and *β*-blockers with vasodilating properties (e.g., the β/a-adrenoblockers carvedilol and labetalol, and β1-blockers with modulation synthesis of NO, nebivolol), with the latter advocated as having a better glucometabolic profile (44).

Calcium channel blockers

Calcium channel blockers (CCB) are efficacious in relieving ischemic symptoms, and verapamil and diltiazem may prevent reinfarction and death (45,46). There are two types of CCBs:

- *Nondihydropyridine.* These drugs (verapamil and diltiazem) are less selective and lower heart rate by slowing sinoatrial (SA) and AV nodal conduction and depress contractility. Due to their negative inotropic effect they are avoided in uncompensated heart failure.
- *Dihydropyridine.* This class of drug (amlodipine, nifedipine, felodipine, isradipine, nicardipine, nisoldipine) lowers BP and myocardial wall tension thereby reducing myocardial oxygen consumption. Their vasodilatory effect increases coronary blood flow and improves the myocardial oxygen imbalance that causes angina (47). In so doing these drugs have been shown to reduce frequency of angina, the need of nitrates, and extend exercise tolerance through a reduction in ischemic changes on treadmill and ECG (48,49). Amlodipine, in particular, has independent action in relieving diastolic dysfunction other than a reduction in BP (50). All drugs in this class have the potential to cause reflex tachycardia which can be blunted with adjunct use of *β*-blockers. They can also replace *β*-blockers, if not tolerated or where they are contraindicated as in severe obstructive airways disease.

Ranolazine

Ranolazine is an inhibitor of the late sodium channel current with antianginal effects and the additional benefit of improving glycemic control (51). It reduces angina symptoms in stable CAD as monotherapy (Monotherapy Assessment of Ranolazine In Stable Angina [MARISA]) trial (52) or in combination with *β*-blocker or a calcium-channel blocker (Combination Assessment of Ranolazine In Stable Angina [CARISA]) and ERICA (Efficacy of Ranolazine In Chronic Angina) trials (53,54).

Ranolazine has also been shown to decrease hemoglobin A_{1c} (HbA_{1c}) levels in patients with T2DM treated for chronic angina (55). Thus, ranolazine may be particularly well suited for treating CAD in patients with T2DM. A trial of 949 CAD patients with T2DM (56) and stable angina showed that the benefits of ranolazine were more prominent in patients with higher than lower HbA_{1c}. The major study limitation was that the absolute effects, although statistically significant, were small. Ranolazine resulted in only 0.5 fewer episodes of angina and 0.4 fewer sublingual nitroglycerin tablets used per week. Quality of life measures were

not statistically significantly altered. While the clinical relevance of such slight absolute differences may be questioned, the findings in this stable CAD population provided proof of concept that ranolazine with a unique mechanism of action is beneficial, can be added to other well-established antianginal drugs, and is particularly effective with higher HbA_{1c} levels. This is especially relevant for CAD patients with DM, who may have more limited benefits from revascularization and rely to a greater extent on medical management.

The mechanism(s) for why ranolazine had greater benefits in patients with higher HbA_{1c} levels is as yet unknown. Improvement of endothelial function in patients with poorer control of DM and more severe CAD may be contributory as ranolazine improved endothelial function in a small study of patients with DM (57). Although decreasing angina frequency and duration are both important in improving quality of life, it will be important to establish whether ranolazine can reduce myocardial ischemia as well, as this is a powerful determinant of outcomes and prognosis. The TERISA study is the first such study showing a differential and beneficial effect on angina in patients with DM and further studies will be required to confirm if ranolazine has preferential benefits in DM that are related to this drug class and/or related to improving glycemic control. This would help to determine the appropriate combination of drugs and to design new therapies that specifically target CAD in patients with DM.

Ivabradine

Ivabradine is a specific, heart-rate lowering, antianginal drug that works through inhibiting the I_f current – the primary modulator of spontaneous diastolic depolarization in the sinus node. Ivabradine is indicated in the treatment of chronic stable angina in CAD patients with a contraindication or intolerance to β-blockers, or in combination with β-blockers if the patient remains symptomatic or has a heart rate >70 bpm, especially if there is also left ventricular (LV) dysfunction. It can be used in selected patients with intolerance or contraindication to β-blockers. High heart rate is associated with a worse outcome in patients with DM (58) and ivabradine is effective in preventing angina in these patients without any safety concerns or adverse effects on glucose metabolism (59,60). The $BEAUTI_fUL$ trial showed that ivabradine decreased the chances of MI and need for revascularization in stable chronic angina. However, there was no direct evidence related to improvement of angina in the diabetic population.

Trimetazidine

Trimetazidine is a novel drug (a mitochondrial enzyme, 3-ketoacyl coenzyme A thiolase [3-KAT] inhibitor) and a metabolic modulator that improves myocardial energetics at several levels (61). It increases myocardial glucose utilization, minimizes free radical production, and protects against intracellular calcium overload and acidosis. The TACT study confirmed the safety of adding trimetazidine to ongoing therapy resulting in increased exercise tolerance with lower angina frequency (62). However, no direct evidence is available for its effective use in diabetic population.

Prevention of adverse cardiovascular events

In patients with chronic stable angina, the main determinants of adverse outcomes are those related to thrombotic events and onset or progression of ventricular dysfunction. The goals of therapy are therefore to stabilize plaque and prevent progression and prevent or reduce damage from plaque rupture and thrombotic complications. Preventive management includes lifestyle changes, pharmacologic intervention, and in individuals with a large area of ischemic myocardium, appropriate revascularization.

Angiotensin-converting enzyme (ACE) inhibitors

ACE inhibitors are effective in improving mortality and morbidity both in symptomatic and asymptomatic angina in diabetic patients. All patients with DM and stable CAD are recommended an ACE-I (63) largely on the basis of the HOPE study, which showed a 25% reduction in MI, stroke, or cardiovascular death for patients with known vascular disease or DM randomized to placebo or ramipril. This finding was consistent in the prespecified subgroup of patients with DM (64).

A proportionately similar trend to benefit was observed in the subgroup of patients with DM in the EUROPA trial with perindopril in stable CAD, which recruited a population at lower cardiovascular risk (65). The ONTARGET trial (66) compared ramipril and the angiotensin receptor blocker (ARB), telmisartan in a high-risk population similar to that in HOPE. In this head-to-head comparison, telmisartan was found to be

equivalent to ramipril as regards the primary outcome – a composite of death from cardiovascular causes, MI, stroke, or hospitalization for heart failure – while a combination of the two drugs caused adverse events without any increase in benefit. On the basis of this study, it is reasonable to use either ACE-I or ARBs in patients with CAD and DM but the combination should be avoided. Some small studies have shown ACE inhibitors to enhance the hypoglycemic effects of oral hypoglycemic agents (67,68) but these preliminary findings have not been proven in large patient cohorts.

Lipid-lowering therapy

All lipoprotein classes are deranged in T2DM with the two core components affected being a moderate elevation of fasting and nonfasting triglycerides (TGs) and low HDL-C. A wealth of data from case-control, mechanistic, genetic, and large observational studies indicates that a causal association exists between elevation of triglyceride-rich particles and their remnants, low HDL-C, and CVD risk (69,70). Data from statin trials strengthen the position of low HDL as an independent CVD risk marker, even in patients with an LDL-C level that is not elevated (71,72). Data from the FIELD study and ACCORD demonstrated that cardiovascular event rates were significantly higher in those with dyslipidemia (LDL-C 2.6 mmol/L [100 mg/dL], TG ≥2.3 mmol/L and HDL-C ≤0.88 mol/L) (73,74). In FIELD (68), the baseline variables best predicting CVD events over a 5-year follow-up were lipid ratios (non-HDL/HDL-C and total/HDL-C). Apo B–Apo A is related to CVD outcomes, but this ratio was not superior to traditional lipid ratios.

Comprehensive and consistent data exist on the mechanism of action and efficacy of statins in the prevention of CVD events in T2DM (75). The benefits of statin therapy in lowering LDL-C and reducing CVD events are seen in all subgroup analyses of major RCTs (76). In a meta-analysis of 14 RCTs covering 18,686 people with DM, the mean duration of follow-up was 4.3 years, with 3247 major vascular events. The study reported a 9% reduction in all-cause mortality and a 21% reduction in the incidence of major vascular outcomes per mmol/L of LDL-C lowering (RR 0.79; 99% Cl 0.72–0.87; *P* 0.0001), similar to that seen in non-DM. The magnitude of the benefit was associated with the absolute reduction in LDL-C, highlighting a positive relationship between LDL-C and CVD risk, and was seen at a starting LDL-C as low as 2.6 mmol/L (77).

Reports from larger RCTs confirm statins to be safe and well-tolerated with the frequency of adverse events, except for muscle symptoms, being rare. In the majority of cases of myopathy or rhabdomyolysis, there are drug interactions with a higher-than-standard dose of statin (78,79). The combination of gemfibrozil and statins should be avoided due to pharmacokinetic interaction, but there are no safety issues with fenofibrate and statins (80).

A meta-analysis of five statin trials reported that the risk of new-onset DM increased with intensive statin (atorvastatin or simvastatin 80 mg daily) therapy (OR 1.12; 95% Cl 1.04–1.22; I^2= 0%), compared with moderate (simvastatin 20 mg or pravastatin 40 mg) doses (81).

In the intensive group, two additional cases of new-onset DM per 1000 patient years were observed, whereas the number of CVD events was reduced by 6.5 cases.

Antiplatelet drugs

Progression of atherothrombosis is accelerated by platelet activation which is increased in patients with DM (82). Increased platelet activation is associated with increased whole blood thrombogenicity (vulnerable blood) in patients with DM and stable CAD (83,84) and is reduced with addition of clopidogrel (85). The increased risk of bleeding associated with antiplatelet drugs prevents their widespread use in unselected cohorts of patients with DM and there is no direct evidence of benefit of aspirin in primary prevention. In patients with DM and stable angina, there is unequivocal evidence of the benefit of long-term, low-dose aspirin in significantly reducing serious vascular events (86). There is no evidence for the addition of a second (P2Y12 inhibitor) antiplatelet drug for secondary prevention in stable CAD. For such patients, undergoing percutaneous coronary revascularization, the duration of a second agent is determined by the type of coronary stent inserted (1 month for bare metal and 12 months for drug-eluting stents [DES]). Following ACS, the role of an additional antiplatelet agent for 1 year is recommended (87).

Lifestyle changes

Risk factor(s) for CAD have complex relationship with the pathophysiology of the disease (88). Patients with

two or more risk factors may have fourfold greater risk of having CAD, with three risk factors an 8- to 20-fold increased risk of having CAD (89). A recent UK Health and Lifestyle Survey reported that modest changes in health behavior could delay aging by 12 years with a 25% reduction in risk of death (90). Therefore, identifying risk factors and taking necessary preventative measures have been shown to improve prognosis in chronic stable angina (91). The following is a brief summary of recommendations for lifestyle changes in patients with DM and chronic stable angina.

- Patient education. Patients are strongly recommended to modify lifestyles such as daily physical activity (92,93), reduced intake of saturated fats (<7% of total calories), trans fatty acids (<1%), and cholesterol (<200 mg/d).
- Smoking cessation. Stepwise strategy for smoking cessation is recommended by following 6 As (Ask, Advise, Assess, Assist, Arrange, and Avoid).
- Weight control. BMI should be assessed at every visit and patients counseled to maintain BMI between 18.5 and 24.9 kg/m^2. Similarly, waist circumference should be assessed and advised to be <102 cm in men and 88 cm in women.
- Physical activity. All patients should encourage 30–60 minutes of moderate intensity aerobic exercises at least 5 days per week.
- Eating "healthy diet." Adhering to 4 of 5 important dietary components:
  - low sodium intake <1.5 g/d
  - sugar sweetened beverage intake <36 oz. weekly
- ≥4.5 cups of fruits and vegetables/d
- ≥three 1 oz. servings of fiber-rich whole grains/d
- ≥two 3.5 oz. servings of oily fish/week.

Revascularization

Revascularization in diabetic patients is complicated by more diffuse atherosclerosis involvement and a higher propensity to develop restenosis after PCI and saphenous graft occlusion after coronary artery bypass graft surgery (CABG) and inexorable atherosclerotic progression (94).

These changes result in a higher operative risk and long-term mortality in patients with T2DM, irrespective of revascularization modality (95). Trial evidence on the effect of myocardial revascularization in patients with DM has lagged behind continued development of PCI, CABG, and pharmacological treatments, making it difficult to establish adequate comparisons (96,97).

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial (98) was a randomized comparison of myocardial revascularization, either with CABG or PCI, versus optimal medical treatment (OMT) – in DM patients with stable CAD, considered eligible for either PCI or CABG. Once the most appropriate revascularization technique had been chosen, patients were randomized to OMT alone or to revascularization plus OMT. At 5 years, there were no significant differences in the combined end point of death, MI, or stroke between the OMT (12%) and revascularization (12%) arms. In the surgical group, freedom from major adverse cardiac and cerebrovascular events (MACCE) was significantly higher with CABG (78%) than with OMT alone (70%, $P = 0.01$), but there was no difference in survival (CABG 86%; OMT 84%; $P = 0.33$). In the PCI arm (patients in PCI group had less-extensive CAD than in the CABG group), there were no significant differences in MACCE or survival between PCI and OMT. During subsequent follow-up, 38% of the patients assigned to OMT underwent at least one revascularization for symptomatic reasons, compared with 20% in the revascularization stratum. The study showed that in patients with diabetes and stable CAD, an initial conservative strategy with OMT saved about 80% of interventions over the next 5 years. However, initial coronary revascularization was superior to medical therapy in maintaining freedom from angina, preventing new onset of angina and arresting worsening of angina in diabetic patients during 3 years of follow-up (99). The difference was remarkable especially during the first year after randomization but diminished over the period. Also, the revascularization group had significantly lower need for subsequent revascularization over the time but the magnitude of benefit initially seen in the PCI group diminished over the period.

Overall, except in specific situations such as left main coronary artery stenosis ≥50%, proximal LAD stenosis or triple vessel disease with impaired LV function, myocardial revascularization in patients with DM did not improve survival when compared with medical treatment. When extrapolating these results into practice, it is important to remember criteria used to

select patients. Patients were excluded if they required immediate revascularization or had left main coronary disease, a creatinine level >2.0 mg/dL (>177 mmol/L), HbA_{1c} >13.0%, class III–IV heart failure, or if they had undergone PCI or CABG within the previous 12 months.

Percutaneous coronary revascularization versus coronary artery bypass graft surgery

The literature on CABG versus PCI is limited by confounder bias in registries, the ongoing technological development in this field, for example, DES, bioabsorbable stents, robotic surgery, and, apart from the FREEDOM (100) and CARDIA trials (101), a lack of prospective RCTs. The result is that much of the available information derived from subgroup analyses in trials in populations in which patients with DM may be relatively few and/or poorly defined.

Even with these limitations, higher repeat revascularization rates after PCI are consistently reported in DM patients included in RCTs comparing CABG and PCI. A meta-analysis based on individual data from 10 RCTs (7812 patients) comparing both types of revascularizations reported a distinct survival advantage for CABG in DM patients (91). The 5-year mortality was 20% with PCI, compared with 12% with CABG (OR 0.7; 95% CI 0.6–0.9), but interestingly, no difference was found for patients without DM; the interaction between the presence of DM and type of revascularization was significant. The Coronary Artery Revascularization in Diabetes (CARDia) trial was the first study to compare revascularization strategies specifically in the diabetic population (101). The introduction of DES coincided with the enrolment period, leading to a mixed use of bare metal stents (BMS) (31%) and DES (69%). After 1 year there was a nonsignificantly higher rate of the composite of death, MI, and stroke (driven by a higher rate of MI) and significantly higher rates of repeat revascularization in the PCI group (2% vs. 12%, $P<0.001$). The conclusions were challenged by the failure to recruit to target and the trial failed to reach the numbers intended to adequately power the study.

In the SYNTAX trial (102–104), only DES (paclitaxel-coating) was mandated and the rate of MACCE after 1 year was twice as high with PCI as it was with CABG. In the prespecified subgroup with DM, the relative risk for repeat revascularization after 1 year was even higher (RR 3.2; 95% CI 1.8–5.7; $P < 0.001$). In patients with DM and complex lesions giving rise to high SYNTAX scores, 1-year mortality was higher in the DES group (14% vs. 4%; $P = 0.04$) (94). After 5 years of follow-up, the rates of MACCE were significantly higher in patients with DM patients undergoing PCI compared to CABG (PCI: 46.5% vs. CABG: 29.0%; $P<0.001$). Qualitatively similar findings were reported for repeat revascularization (PCI: 35.3% vs. CABG: 14.6%; $P< 0.001$). However, there was no difference in the composite of all-cause death, stroke, MI (PCI: 23.9% vs. CABG: 19.1%; $P = 0.26$). The conclusion from the study was that, although PCI was a potential treatment option in patients with less complex lesions, CABG should be the revascularization choice for patients with complex anatomic disease, especially with concurrent DM.

While the results from the SYNTAX trial seemed to provide clarity in the selection of revascularization strategy in patients with DM, in contrast, an analysis of DM patients included in the AWESOME (105) randomized trial and registry included high-risk patients for CABG (prior CABG, recent MI, LVEF 30% or intra-aortic balloon pump treatment) but showed no significant difference in 3-year mortality between revascularization techniques. Recent large patient registries report better outcomes in patients with DM treated with CABG, compared with DES, in terms of mortality but at the expense of a higher stroke rate (106). An analysis of 86,244 patients ≥65 years of age undergoing CABG and 103,549 patients undergoing PCI from 2004 to 2008 revealed 4-year survival to be significantly higher with surgery with the association of surgery and improved survival being most marked in insulin-treated DM (107). The MAIN COMPARE study reported long-term outcomes of 1474 patients with unprotected left main stenosis, treated with DES or CABG. In this specific setting, a subgroup analysis comparing patients with (n = 507; 34%) and without DM did not reveal significant interactions between treatment outcomes and the presence or absence of DM after adjustment for covariates (108).

The FREEDOM trial randomized 1900 patients (majority with three-vessel disease) to treatment with CABG or PCI with any drug-eluting stents after FDA approval. All patients were prescribed currently recommended medical therapies for the control of LDL-C, systolic BP, and HbA_{1c}. The primary outcomes measure was a composite of total mortality and nonfatal MI or stroke. After a median of 3.8 years, the primary outcome

occurred more frequently in the PCI group ($P = 0.005$), with a 5-year rate of 26.6%, compared with 18.7% in the CABG group. The benefit of CABG was driven by differences in both MI ($P< 0.001$) and mortality ($P = 0.049$) (89). A meta-analysis of trials involving revascularization in diabetes mellitus concluded that patients with multivessel CAD and diabetes derived greater benefit from surgical revascularization (109).

Summary

The clinical presentation of myocardial ischemia in patients with DM can range from typical chest pain to exertional breathlessness to asymptomatic silent ischemia. Given the increased incidence of CAD in patients with DM, it is disappointing that routine screening of patients with DM has proved unhelpful. Once ischemia has been diagnosed, its management follows the same principles as in the nondiabetic population, namely symptom control and improving prognosis through reducing ischemic burden. The only pharmacologic agent that appears to have differential (increased benefit) effect of patients with T2DM is ranolazine and further studies are required to elucidate the mechanism of this increased benefit. Lifestyle changes are central to the management of patients with diabetes, and the important and long-term benefits in controlling the progression of macrovascular disease cannot be overemphasized. While data for revascularization continue to evolve, current evidence suggests that in diabetic patients with multivessel CAD and high SYNTAX scores, surgical revascularization offers better long-term outcomes.

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