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Coronary artery disease and diabetes mellitus

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SUMMARY

Coronary artery disease (CAD) is a major determinant of the long-term prognosis among patients with diabetes mellitus (DM). DM is associated with a 2 to 4-fold increased mortality risk from heart disease. Furthermore, in patients with DM there is an increased mortality after MI, and worse overall prognosis with CAD. Near-normal glycemic control for a median of 3.5 to 5 years does not reduce cardiovascular events. Thus, the general goal of HbA1c <7% appears reasonable for the majority of patients. Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes, and is an independent cause of excess morbidity and mortality. Statins are effective in reducing major coronary events, stroke, and the need for coronary revascularization.

Selection of the optimal myocardial revascularization strategy for patients with DM and multivessel coronary artery disease is crucial and requires a multidisciplinary team approach ('heart team'). Large scale clinical trials have shown that for many patients with 1- or 2-vessel coronary artery disease, there is little prognostic benefit from any intervention over optimal medical therapy (OMT). PCI with drug-eluting or bare metal stents is appropriate for patients who remain symptomatic with OMT. Randomized trials comparing multivessel PCI to coronary artery bypass grafting (CABG) have consistently demonstrated the superiority of CABG in reducing mortality, myocardial infarctions and need for repeat revascularizations.

Keywords

Blood Glucose; Coronary Disease; Diabetes mellitus; Hypoglycemic Agents; Revascularization; Statins

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Introduction

Diabetes mellitus (DM) has reached epidemic proportions worldwide, and its prevalence is rising.^{1,2} The implications of a diagnosis of DM are as severe as a diagnosis of coronary artery disease (CAD). Cardiovascular mortality in all age groups and for both sexes rises equivalently with DM or a history of myocardial infarction (MI) and the two are profoundly synergistic³ (Figure 1). In addition, DM (especially type 2 DM), is associated with clustered risk factors for cardiovascular disease (CVD). Amongst adults with DM there is a prevalence of 75% to 85% of hypertension, 70% to 80% for elevated LDL, and 60% to 70% for obesity.⁴ CAD is the main cause of death in both type 1 and type 2 DM,⁵ and DM is associated with a 2 to 4-fold increased mortality risk from heart disease. Over 70% of people >65 years of age with DM will die from some form of heart disease or stroke.² Furthermore, in patients with DM there is an increased mortality after MI, and worse overall long-term prognosis with CAD.^{6,7}

In the United States, approximately one third of all percutaneous coronary intervention (PCI) procedures are performed on patients with DM and ~25% of patients undergoing coronary artery bypass graft (CABG) surgery have DM⁵; the outcomes of these procedures is less effective than in those without DM. DM modifies the response to arterial injury, with profound clinical consequences in terms of risk for restenosis⁸ and stent thrombosis.⁹ Although there has been considerable improvement in the management of patients with CAD, coronary event rates remain heightened among patients with DM.^{2,10-12} Therefore, optimal medical therapy (OMT) and appropriate selection of myocardial revascularization strategy is critical for patients with DM. The following review summarizes the current evidence regarding the effectiveness of various medical therapies and revascularization strategies in patients with DM.

Glycemic control and cardiovascular outcomes

DM is a fascinating disease in that while it has been known since antiquity the disease we refer to can only be dated to the era after the wide-spread use of insulin. Prior to the introduction of insulin replacement DM was an almost universally fatal disease that primarily struck children. The DM of today, with all of its chronic manifestations, is the associated consequence of lifesaving and life-prolonging effects of insulin and naturally many have wondered how “tight” control of blood sugar with precise insulin dosing would affect cardiovascular risk. The results have been sobering; in general, tight glycemic control is associated with an increased risk for hypoglycemia but minimal to no benefit on mortality. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was designed to test whether treatment targeting nearly normal glycemic control reduces the risk of cardiovascular events in type 2 DM. More than ten thousand patients were randomized to either a standard treatment strategy that targeted HbA1c levels between 7% and 8% or an intensive strategy that sought to attain an hemoglobin (Hb) A1c <6.0%. The median HbA1c with the standard strategy was 7.5%; the intensive strategy achieved a median HbA1c of 6.4%.¹³ Yet, the intensive strategy was associated with 22% increase in all-cause mortality and the study was stopped after a median follow-up of 3.4 years.

The Action in Diabetes and Vascular Disease: A Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial randomized 11,140 participants to a strategy of intensive glycemic control (with primary therapy being the sulfonylurea gliclazide and additional medications as needed to achieve a target HbA1c of <6.5%) or to standard therapy, with the glycemic target set according to “local guidelines”. The median HbA1c levels achieved in the intensive and standard arms were 6.3% and 7.0%, respectively. Intensive treatment produced a relative reduction of 10% in the primary composite outcome of major macrovascular and microvascular events (HR, 0.90; 95% CI, 0.82 to 0.98; $P=0.01$), primarily as a consequence of a reduction in nephropathy (a microvascular complication). However, when major macrovascular events were considered separately (MI, stroke, and cardiovascular death), there was no observed significant reduction (HR, 0.94; 95% CI, 0.84 to 1.06; $P=0.32$).¹³

The Veterans Affairs Diabetes Trial (VADT) randomized 1791 participants with type 2 DM uncontrolled on insulin or maximal-dose oral agents (median entry HbA1c, 9.4%) to intensive glycemic control (goal HbA1c, <6.0%) or standard glycemic control, with a planned HbA1c separation of at least 1.5%.¹⁴ Over a 5.6 year follow up period there was no significant difference in the primary outcome of a composite of MI, stroke, cardiovascular death, revascularization, hospitalization for heart failure, and amputation for ischemia.

A large retrospective cohort study from the UK General Practice Research Database showed a U-shaped pattern of risk association between HbA1c and all-cause mortality and progression to large-vessel disease events among patients with type 2 DM.¹⁵ A HbA1c of approximately 7.5% was associated with the lowest risk and an increase or decrease from this mean HbA1c value was associated with a heightened risk of adverse outcomes (Figure 2).

The most compelling message from these studies is that near-normal glycemic control for a median of 3.5 to 5 years does not reduce cardiovascular events within that period.¹⁶ The contribution of glucose lowering to the reduction of macrovascular events in the ADVANCE and ACCORD trials appears to be minimal. It may very well be that even 90 years after insulin’s introduction as a therapeutic modality we are still unclear on the drivers of cardiovascular morbidity as a chronic manifestation of DM.

For the prevention of macrovascular disease, the general goal of HbA1c <7% appears reasonable (ACC/AHA, Class IIb recommendation; Level of Evidence: A).¹⁷ For selected individual patients, lower HbA1c goals may be reasonable in an attempt to reduce microvascular complications (low risk of hypoglycemia short duration of diabetes, long life expectancy, and no significant cardiovascular disease). Yet, it has also become clear that the potential risks of intensive glycemic control may outweigh its benefits in patients with a long duration of diabetes, known history of severe hypoglycemia, advanced atherosclerosis, and advanced age/frailty. Here less stringent HbA1c goals may be appropriate (7.5–8.0% or possibly even slightly higher).^{17,18}

Antidiabetic drug safety

Until recently, insulin and then oral agents based on metformin and sulfonylureas dominated the therapy of DM. There are now several additional classes of drugs approved for diabetes management: α -glucosidase inhibitors, thiazolidinediones, meglitinides, glucagon-like peptide analogues, amylin analogues, dipeptidyl peptidase IV inhibitors and sodium-glucose cotransporter 2 (SGLT-2) inhibitors.¹⁹ Most oral diabetes medications reduce HbA1c levels by a similar amount, by approximately 1 absolute percentage point.²⁰ Glycated hemoglobin, however, may not be a valid surrogate for assessing either the cardiovascular risks or benefits of diabetes therapy,²¹ and the long-term safety of these newer drugs with respect to cardiovascular disease (the leading cause of illness and death among patients with diabetes) remains poorly characterized. In addition, antidiabetic agents may have multiple, additional potential effects on risk factors for CAD and on cardiac function (Table 1).

Concerns have been raised that some antidiabetes agents may impart greater cardiovascular risk. The University Group Diabetes Project study suggested increased CV risk in patients treated with tolbutamide, a first-generation sulfonylurea. These results have been widely criticized based on study design flaws.²² A meta-analysis of clinical trials of rosiglitazone (Avandia), a thiazolidinedione, pointed to an increased risk of MI,²³ although the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study did show an increased risk of major adverse cardiovascular events (MACE).²⁴

The initial concern with rosiglitazone led the FDA to issue an updated Guidance for Industry in 2008 requiring preapproval and post approval studies for all new antidiabetic drugs to rule out excess cardiovascular risk. In a postmarketing trial, the two-sided 95% CI for the estimated increased risk (risk ratio) should be less than 1.3.²⁵

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial assessed therapeutic strategies rather than any specific drug. No safety concerns were seen for the insulin-sensitizing group, in which >60% received thiazolidinediones, predominantly rosiglitazone (55%).²⁶ Notwithstanding, given that other options are now available, the use of rosiglitazone is not recommended.²⁷ Newer antidiabetic agents, such as, agonists of the glucagon-like peptide-1 (GLP1) receptor or dipeptidyl peptidase 4 (DPP4) inhibitors, which prevent the breakdown of endogenous GLP1, have shown beneficial effects in patients undergoing angioplasty and CABG in small studies.^{28,29} However, in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR), the DPP-4 inhibitor saxagliptin did not change the primary composite endpoint of cardiovascular death, myocardial infarction, or ischemic stroke, when added to the standard of care in patients at high risk for cardiovascular events.³⁰ Although saxagliptin clearly met the FDA guidance for cardiovascular safety, therapy with the drug was associated with an unexpected increased risk of hospitalization for heart failure (especially in patients with high baseline BNP levels) and a higher frequency of hypoglycemia.³⁰ Similarly, in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, the DPP-4 inhibitor alogliptin was neutral with regard to major cardiovascular events that in patients with type 2 diabetes and cardiovascular disease or high cardiovascular risk, but met the FDA guidance for cardiovascular safety.³¹ Currently, there

is no sufficient evidence to definitively support one drug or combination of drugs over another for long-term clinical outcomes of mortality and macrovascular and microvascular complications of diabetes.^{20,32}

Hypoglycemia and Mortality

Iatrogenic hypoglycemia is the limiting factor in the glycemic management of DM, and classically arises from the interplay of mild-to-moderate absolute or even relative therapeutic hyperinsulinemia and compromised physiological and behavioral defenses against falling plasma glucose concentrations.³³ Hypoglycemia is a substantial, independent cause of excess morbidity and mortality. In the ACCORD trial, severe hypoglycemia was associated with increased mortality by 2 and 4-fold in the intensive and conventional groups, respectively. However, hypoglycemia was not identified as the cause for this excess mortality in the intensive group.³⁴

In the ADVANCE trial, severe hypoglycemia was associated with excess cardiovascular events and total mortality.³⁵ However, neither a close temporal relationship nor a dose–response relationship was observed between hypoglycemic events and subsequent cardiovascular or fatal events. Therefore, hypoglycemia might be a marker for patient-related disorders or complications, which could predispose patients to an excess risk of coronary heart disease.^{34,35}

Plausible mechanisms by which hypoglycemia might cause cardiovascular events or lead to death from cardiovascular disease include sympathoadrenal activation, abnormal cardiac repolarization, increased thrombogenesis, inflammation, and vasoconstriction leading to cardiac ischemia or fatal arrhythmia during recognized or unrecognized episodes of hypoglycemia.^{36,37} Although the relationship in hospitalized patients with acute MI between hypoglycemia and cardiovascular outcomes is complex,³⁸ there was a clear J-shaped relationship between glucose values and adverse outcomes, including increased mortality.^{39,40} In this context, hypoglycemia has been shown to lower myocardial blood flow reserve⁴¹ and increase experimental infarct size.⁴² Although it is reasonable to suspect that iatrogenic hypoglycemia contributes directly to the excess mortality during intensive glycemic therapy, especially during acute ischemia, the association may represent increased vulnerability of people who are prone to hypoglycemia to other serious health outcomes due to the coexistence of other risk factors^{35,38} or hypoglycemia may be a marker for more critical illness.⁴³ Notwithstanding, these data provide compelling reasons to minimize the risk of hypoglycemia in patients with diabetes and CAD.

The use of insulin infusions to control hyperglycemia or to provide metabolic support in face of stress is falling off as severe hypoglycemia (<2.2 mmol/L [40 mg/dL]) occurs frequently (5%–17%)^{44,45} and is associated with higher mortality.⁴⁶ There is no additional benefit from the lowering of blood glucose levels below the range of approximately 140 to 180 mg/dL.^{47–49} For the majority of critically ill patients, the American Diabetes Association recommends initiating insulin therapy for treatment of persistent hyperglycemia, starting at a threshold of no greater than 180 mg/dl (10.0 mmol/l), and aiming for glucose range of 140–180 mg/dl (7.8–10.0 mmol/l).⁴⁷ Similar recommendations

were provided by the American College of Physicians⁴⁸ and the American Heart Association (Figure 3).⁴⁹

Management of hyperlipidemia in patients with DM

Hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the cornerstone of lipid-associated cardiovascular-risk reduction, with established benefits in reducing clinical events in patients with diabetes shown in a multitude of trials. The Cholesterol Treatment Trialists' (CTT) Collaboration analysis of data from 18686 individuals with diabetes (1466 with type 1 and 17 220 with type 2) in the context of 14 randomized trials of statin therapy, showed that statin therapy reduced the 5-year incidence of major vascular events by about a fifth per mmol/L reduction in LDL cholesterol, with similar proportional reductions in major coronary events, stroke, and the need for coronary revascularization.⁵⁰

For *primary prevention*, patients with DM ages 40 to 75 years with an LDL-C 70 to 189 mg/dL and without clinical cardiovascular disease, are one of the major statin benefit groups. Among the four randomized controlled trials focused exclusively on primary prevention, the highest rate of cardiovascular events occurred in Collaborative Atorvastatin Diabetes Study (CARDS),⁵¹ which exclusively enrolled a primary prevention population with diabetes. The CTT meta-analyses also supports the use of statins to reduce the risk of cardiovascular disease in individuals with type 1 or 2 diabetes^{50,52} (Figure 4). Thus, a high level of evidence supports the use of moderate-intensity statin therapy in all primary-prevention-eligible adults age 40 to 75 years with DM (Table 2). For *primary prevention* in individuals with DM (both type-1 and type-2), the estimated 10-year cardiovascular risk can also be used to guide the intensity of statin therapy; such that when the estimated 10-y CVD risk is $\geq 7.5\%$, high-intensity statin can be used. The percent reduction in LDL-C can be used as an indication of response and adherence to therapy, but is not in itself a treatment goal.⁵³ For *secondary prevention*, high-intensity statin therapy should be initiated for adults ≥ 75 years of age who are not receiving statin therapy or the intensity should be increased in those receiving a low- or moderate-intensity statin.⁵³ Combination therapy does not provide additional cardiovascular benefit above statin therapy alone and is not generally recommended.⁵⁴

Statin use and risk of diabetes

There has recently emerged a concern that statin use may be associated with the development of DM. A collaborative meta-analysis of 13 randomized placebo-controlled trials with more than 90,000 participants found a small, 9% increased risk for incident diabetes after four years of statin treatment, particularly in older people.⁵⁵ For 255 patients (95% CI 150–852) treated for 4 years with a statin, one additional patient would develop diabetes. Another meta-analysis showed that intensive-dose statin therapy is associated with a somewhat higher risk than moderate dose therapy.⁵⁶ In higher risk secondary prevention patients with established CAD, the diabetes risk associated with statin therapy is low in absolute terms when compared with the reduction in cardiovascular events. Based on these studies, the FDA added a warning regarding diabetes risk to the labeling of statins.⁵⁷

In the randomized, placebo controlled Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, there was a modest risk of developing diabetes on statin therapy that was limited to patients who had preexisting biochemical evidence of impaired fasting glucose or multiple components of metabolic syndrome.⁵⁸ However, even in the setting of this primary prevention trial, the cardiovascular and mortality benefits of statin therapy exceeded the diabetes hazard in the trial population as a whole as well as among those at higher risk for developing diabetes.

Overall, the risk of DM is ~1 excess case per 1000 individuals treated with a moderate-intensity statin for 1 year and ~3 excess cases per 1000 individuals treated with a high-intensity statin treated patients for 1 year.⁵³ Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus. Those who develop diabetes mellitus during statin therapy should continue statin therapy to reduce their risk of CVD events.⁵³ To date, a potential mechanism to explain the findings of a higher incidence of DM with statin therapy compared with placebo, and intensive-dose therapy compared with moderate dose therapy, has not been clearly identified.

Coronary revascularization in patients with DM

Revascularization versus Medical Therapy

Patients with DM and CAD are at high risk of cardiovascular events regardless of symptoms.⁵⁹ Whether such patients with stable CAD should undergo prompt revascularization is an important clinical question with broad implications for risk stratification and treatment.⁶⁰ As such, the BARI 2D trial tested the hypothesis that in patients with DM and stable CAD, prompt revascularization with either CABG or PCI, would reduce long-term rates of death and cardiovascular events as compared with OMT alone. BARI-2D randomized patients with demonstrated ischemia who were asymptomatic or who had mild to moderate symptoms, and documented CAD by angiography. The appropriate method of revascularization for each patient (PCI or CABG) was determined a priori by the responsible physician, resulting in a population of patients with a much greater atherosclerotic burden in the CABG stratum. The 5-year survival rate was 88.3% among patients in the revascularization group and not statistically different in the medical-therapy group (87.8%). Similarly, the major cardiovascular event rate did not differ significantly between the revascularization and the OMT groups. As compared with OMT, patients who underwent CABG (but not PCI) had significantly fewer major cardiac events, mainly a reduction in nonfatal MIs.²⁶

The benefits of revascularization were documented mostly during the year after the intervention, and most importantly were noticeably greater in patients undergoing CABG than PCI (Figure 5).^{26,61} Similarly, in COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), the addition of early PCI to optimal medical therapy did not significantly reduce the risk of death or MI regardless of DM status.⁶²

Use of Drug Eluting Stents in Patients With DM

Although the magnitude of restenosis reduction achieved with drug-eluting stents (DES) is impressive, it is important to recognize that these trials mandated an angiographic follow-up. Revascularization was therefore driven not only by clinical necessity but also by the angiographic appearance of narrowing within the treated segment even in patients who did not have documented ischemia.⁶³ In real world practice, the benefit of DESs in patients with DM appears to be less impressive.⁶⁴ For example, in the Swedish Coronary Angiography and Angioplasty Registry, the numbers needed to treat a diabetic patient with DES to avoid one additional restenosis per year with BMS ranged from 21 to 47 lesions in patients treated with one stent and 11 to 27 in patients with multiple stents.⁶⁵ DES significantly reduced restenosis to half the rate seen with BMS. However, there was no difference in the combined outcome of death or MIs in diabetic patients treated with DES or BMS with up to 4 years of follow-up.⁶⁵

Recent studies evaluated the comparative effectiveness of second-generation DES among diabetic patients.⁶⁰ A post hoc subgroup analysis from 4 pooled randomized trials with 27.6% diabetic patients compared the Xience V everolimus eluting stent (EES) with a first generation DES, Taxus PES (paclitaxol eluting stent, Express and Liberté)⁶⁶ In these 1,869 patients with diabetes, there were no differences in clinical outcomes after 2 years between the first- and newer generation DES.⁶⁶

Data regarding the latest-generation Resolute Zotarolimus Eluting Stent (ZES; with controlled drug release over a longer time period) was analyzed using pooled patient-level data from the 5,130 patients (1,535 with DM). Target vessel failure (TVF) was defined as a composite of cardiac death, target vessel myocardial infarction, and ischemia-driven target vessel revascularization. The rate of TVF in a pre-specified analysis of patients with diabetes at 12 months was 7.8%, considerably less than the predefined DES performance goal of 14.5% ($p < 0.001$).⁶⁷ After 2 years, the cumulative incidence of TLF in patients with noninsulin-treated diabetes was comparable to that of patients without diabetes (8.0% vs. 7.1%). The higher risk insulin-treated DM demonstrated a significantly higher TLF (13.7%). Rates of ST were not significantly different between patients with and without diabetes (1.2% vs. 0.8%). Based on this analysis, the FDA approved the Resolute ZES with specific labeling indication for patients with DM.

Although both of the newer generation DES (i.e., the Resolute ZES and the Xience V) have improved outcomes compared with first-generation DES, there is still an opportunity to improve the treatment of CAD in patients DM, particularly those treated with insulin. Overall, the results emphasize the lack of mechanistic understanding with regard to the antiproliferative drugs eluted by the stent and adverse events after PCI.⁶⁰

Stent Thrombosis after Drug Eluting Stent implantation

The possibility of increased rates of stent thrombosis (ST) after DES has been a matter of concern and can be particularly pertinent to diabetic patients. ST is classified based on the time of the adverse event relative to the index procedure. Early ST refers to the first 30 days after stent implantation and is further stratified into acute (<24 hours) and subacute (24

hours to 30 days). Late ST defines the time interval between 1 month and 1 year after stent implantation; very late ST includes any event beyond 1 year.⁶⁸ After DES implantation, very late ST occurs at a relatively constant rate over time up to at least 5 years after stent implantation.⁶⁹

ST is a multifactorial problem related to patient, lesion, and procedural factors and to the coagulation system and response to anti-platelet therapy.⁶⁸ Delayed healing and impaired endothelialization (i.e., incomplete endothelial coverage of stent struts associated with persistence of fibrin deposits) is a common features of most cases of late and very late ST, which either alone or in combination with chronic inflammation and hypersensitivity reactions, and outward remodeling promote ST.⁷⁰ All of these pathologic processes are amplified in DM and it therefore not surprising that several studies demonstrated higher ST rates in diabetic patients, particularly in insulin-treated patients.^{9,69,71,72}

In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, insulin-requiring DM was a significant independent predictor of definite or probable ST occurring within 30 days (odds ratio, 2.35).⁷³ In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38), patients with DM and acute coronary syndrome (n = 3146) had twice the rate of stent thrombosis than those without DM (2.8% versus 1.4%, $P < 0.0001$), with highest rates among subjects treated with insulin (3.7%, $P < 0.0001$).⁷⁴ In the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, insulin-treated DM was an independent predictor of acute, subacute, late and very late ST.⁷⁵

In a large 2-Institutional Cohort Study of 8,146 patients who underwent PCI with a sirolimus-eluting stents (SES) (n = 3,823) or paclitaxel-eluting stents (PES) (n = 4,323) and were followed up to 4 years after stent implantation, DM was an independent predictor of overall, early, and late definite ST.⁷⁶ Similarly, in the Swedish Coronary Angiography and Angioplasty Registry of almost 74,000 DES and BMS, insulin-treated DM was an independent predictor of ST (RR 1.77).⁷⁷ Finally, in the e-Cypher registry (n = 15157), insulin-dependent DM was an independent predictor of ST at 1-year (2.8-fold risk increase).⁷¹

The increased risk of diabetic patients for ST might be related to the more diffuse nature of atherosclerosis, accompanied by longer lesion lengths, smaller vessel size, and greater plaque burden, which might impose less optimal procedural results. Additionally, the detrimental effects of DM on endothelial function⁷⁸ and platelet function⁷⁹ may also promote the development of ST. However, further studies are needed to elucidate the mechanisms leading to increased ST risk among diabetic patients.

CABG versus PCI in Multivessel CAD

The Bypass Angioplasty Revascularization Investigation (BARI) study compared multivessel angioplasty to CABG in patients with medically treated DM and found a near doubling of mortality at 5-years with PCI (35% vs. 19%, $P=0.003$)⁸⁰. The survival benefit of CABG in patients with diabetes persisted at 10 years (PTCA 45.5% vs. CABG 57.8%,

$P=0.025$)⁸¹. In an analysis based on pooled individual patient data from 10 randomized trials comparing CABG with PCI (median follow-up of 5.9 years), mortality among patients with DM was 30% lower in the CABG group than in the PCI group.⁸² These large differences in mortality underscore the importance of appropriate decisions regarding the mode of revascularization in DM.

However, many cardiologists dismissed the results of these earlier randomized studies as outdated because the advent of DES technology.⁸³ Two contemporary trials comparing PCI with DES to CABG in patients with DM attempted to address this renewed controversy. The pre-specified DM-subgroup analysis (n=452) of SYNTAX (SYnergy Between PCI With TAXus and Cardiac Surgery)⁸⁴ showed that the 5-year composite MACCE rate was significantly higher in patients with DM after PCI compared with CABG (PCI: 46.5% vs CABG: 29.0%; $P < 0.001$) mainly due to an increased risk of repeat revascularization (PCI: 35.3% vs CABG: 14.6%; $P < 0.001$).⁸⁵ However, the difference between PCI and CABG is larger for patients with DM than for those without.

The CARDia (Coronary Artery Revascularization in Diabetes) trial enrolled patients with DM (n=510) with either multivessel CAD or complex single-vessel CAD (ostial or proximal left anterior descending artery disease) in whom coronary revascularization was recommended on clinical grounds⁸⁶. The primary end point was a composite of death, MI, and stroke with a major secondary end point of the composite of the primary outcome and repeat revascularization using a noninferiority design. SES were used in 69% of patients in the PCI arm. The study could not demonstrate noninferiority of PCI for the primary endpoint (10.5% with CABG compared with 13.0% with PCI).

The long-term Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, enrolled 1900 patients with diabetes and multivessel CAD (about as many patients with diabetes as in all previous trials combined) who were randomly assigned to undergo either CABG or PCI with drug-eluting stents (primarily first-generation PES or SES).⁸⁷ After 5 years of follow-up, the 947 patients assigned to undergo CABG had significantly lower mortality (10.9% vs. 16.3%) and fewer myocardial infarctions (6.0% vs. 13.9%) than the 953 patients assigned to undergo PCI. However, patients in the CABG group had significantly more strokes (5.2% vs. 2.4%), mostly those that occurred within 30 days after revascularization. In the CABG group, the primary composite outcome of death, myocardial infarction, or stroke over 5 years was reduced by 7.9 percentage points, or a relative decrease of 30%, as compared with PCI (18.7% vs. 26.6%, $P = 0.005$).⁸⁷ There was no interaction between SYNTAX score and outcomes among the overall population, suggesting that the increased event rate among patients randomized to PCI was not related to the anatomic complexity of disease at the time of revascularization.

Ongoing randomized studies of second-generation DES address important questions about revascularization strategies in patients severe CAD and DM. Currently, however, the results of the FREEDOM and other trials suggest that the comparative effectiveness of CABG and PCI on hard outcomes remains similar whether PCI is performed without stents, with bare-

metal stents, or with drug-eluting stents,⁸³ albeit at the price of an increased risk of nonfatal stroke.

Explaining the mortality benefit of CABG

The protective effects of CABG may be related to the increased restenosis rates following angioplasty in DM and incomplete revascularization associated with multivessel angioplasty.^{88,89} In the BARI study population, 3.1 grafts were placed per patient undergoing CABG, whereas the mean number of successfully treated lesions in the PTCA group was 2.0.⁸⁰ Together with the greater degree of baseline atherosclerosis and the high restenosis rate among diabetic patients, it is likely that a higher proportion of the myocardium remains unprotected and unrevascularized in patients with DM, and a greater proportion of the myocardium becomes ischemic during an acute spontaneous myocardial infarction. The impact of incomplete revascularization may be even more severe because after PCI, progression of diffuse disease in diabetic patients forms new lesions that may cause ischemia and/or symptoms.

The amount of jeopardized myocardium decreases initially following revascularization and increases subsequently with target lesion restenosis, graft failure, or the development of new narrowings in native vessels. Follow-up angiographic analysis of the BARI patients at years 1 and 5 revealed that the total percentage of jeopardized myocardium, defined as the overall percentage of the coronary perfusion territory compromised by stenoses $\geq 50\%$, was higher in diabetic patients.⁹⁰ The mean percentage increase in total jeopardized myocardium was significantly greater in diabetic compared with non-diabetic patients at 1-year protocol-directed angiography (42% versus 24%, $P = 0.05$) and on the first clinically performed (unscheduled) angiogram within 30 months (63% versus 50%, $P = 0.01$) but not at 5-year protocol-directed angiography (34% versus 26%, $P = 0.33$). In contrast, among CABG patients, DM was not associated with an increase in jeopardized myocardium at any angiographic follow-up interval. In this context, DM does not seem to affect the patency of internal thoracic artery (ITA) grafts, or the accelerated atherosclerotic process that characterizes vein grafts.^{91,92} The lower rate of nonfatal MI with surgical revascularization observed in BARI-2D²⁶ is consistent with the hypothesis that, bypass grafts to the mid-coronary vessel treat the culprit lesion and prophylaxes against new proximal disease, progression of proximal narrowing or plaque rupture occurring proximal to a patent graft insertion. Proximal coronary arterial stents however, bare metal and drug-eluting, cannot protect against new disease.⁹³

Graft Selection and Patency in DM patients

DM does not appear to adversely affect patency of ITA grafts.^{91,94} Nonrandomized analyses indicate that bilateral internal thoracic artery (BITA) grafting appears to be particularly important in the diabetic population.⁹⁵ However, the use of BITA results in greater sternal wound complications in patients with DM (especially insulin-treated).^{96,97} Harvesting skeletonized ITA may reduce the risk of sternal wound complications associated with BITA by minimizing the risk of devascularization of the sternum as compared with removal with an attached muscle pedicle.^{95,98} Therefore, some surgeons believe that DM is not a contraindication for skeletonized BITA.⁹⁹ Notwithstanding, presently, it is unclear whether

selective referral of patients with DM for skeletonized BITA grafting despite higher risks of sternal infection is justified.¹⁰⁰

The radial artery (RA) conduits obtained from patients with DM has greater tendency to spasm compared with RAs from patients without DM, and exhibit impaired endothelial function.¹⁰¹ In a randomized trial comparing angiographic RA graft patency vs. SVG patency at 1-year after CABG, there was a significant interaction between graft type and DM; RA grafts had lower patency rate than SVGs in patients with DM and the reverse was true in patients without DM.¹⁰²

Approach to coronary revascularization in patients with DM

While revascularization therapies mechanically address specific local lesions, they all have limited longevity. As discussed, DM is a systemic disease with a vast array of metabolic effects that often escalate with time. It goes without saying then that the optimal therapy for vascular disease in diabetes is optimization of control of diabetes, and there is significant overlap in that drugs and approaches that control DM also regulate atherosclerotic and cardiovascular disease. Yet, almost a century after insulin transformed DM we still do not fully comprehend the breadth and depth of this disease and as such there is both promise of new therapies yet to be appreciated and the challenge of balancing the harm and benefit of tight glucose control. Careful medical therapy is an excellent first-line strategy for coronary disease in patients with DM who are asymptomatic¹⁰³ or with mild symptoms (CCS Class I or II) and less severe CAD (single-vessel or two-vessel CAD not involving the proximal left anterior descending artery).^{26,104} For these patients, it is unlikely that an initial revascularization strategy is better than medical therapy and may even be worse¹⁰⁵. Revascularization can reduce anginal symptoms⁶¹ and may be applied later if medical therapy does not adequately control symptoms (

Figure 5: Annual occurrence of freedom from angina in 1434 patients with angina at entry in BARI-2D. In the PCI stratum, the increase in freedom from angina was documented only at the first year of the follow-up. In the CABG stratum, the freedom from angina was increased during the 5-year follow-up. From Dagenais GR, Lu J, Faxon DP, et al. Effects of optimal medical treatment with or without coronary revascularization on angina and subsequent revascularizations in patients with type 2 diabetes mellitus and stable ischemic heart disease. *Circulation*. 2011;123:1492–1500; with permission.

Figure 6). In patients who require intervention after optimization of medical therapy there is a significantly higher risk of repeat revascularizations with PCI. DES, albeit, is superior to BMS in ischemia-driven repeat revascularization procedures (target lesion revascularization)^{100,106} and is a reasonable approach in these patients (

Figure 5: Annual occurrence of freedom from angina in 1434 patients with angina at entry in BARI-2D. In the PCI stratum, the increase in freedom from angina was documented only at the first year of the follow-up. In the CABG stratum, the freedom from angina was increased during the 5-year follow-up. From Dagenais GR, Lu J, Faxon DP, et al. Effects of optimal medical treatment with or without coronary revascularization on angina and subsequent

revascularizations in patients with type 2 diabetes mellitus and stable ischemic heart disease. *Circulation*. 2011;123:1492–1500; with permission.

Figure 6). But there remains consistently higher repeat revascularization rates after PCI compared with surgical revascularization in patients with DM.^{86,107,108} The surgical approach has better survival, fewer recurrent infarctions and greater freedom from re-intervention for patients with treated DM, moderate to severe symptoms and multivessel CAD^{107,109}, or significant involvement of the proximal left anterior descending or left main coronary artery (Figure 6).^{26,104,109}

Ultimately, no single treatment approach can be applied to all patients given the confluence of chronic obstructive atherosclerosis and the profound divergent metabolic derangements of DM. Decisions regarding potential revascularization must take into account multiple factors and as such require a multidisciplinary team approach ('heart team'). The heart team approach guarantees that all therapeutic options (i.e. OMT, PCI, and CABG) are transparently discussed, and the individual patient preferences are considered in the decision-making process.¹⁰⁹

Trial acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACUITY	Acute Catheterization and Urgent Intervention Triage Strategy
ADVANCE	A Preterax and Diamicron Modified Release Controlled Evaluation
BARI	Bypass Angioplasty Revascularization Investigation
BARI-2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes
CARDia	Coronary Artery Revascularization in Diabetes
CARDS	Collaborative Atorvastatin Diabetes Study
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
EXAMINE	Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care
FREEDOM	Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease
HORIZONS-AMI	Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction
JUPITER	Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes

SAVOR	Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus
SYNTAX	SYnergy Between PCI With TAXus and Cardiac Surgery
TRITON-TIMI 38	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38
VADT	Veterans Affairs Diabetes Trial

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KEY POINTS

- Large clinical trials have shown that a near-normal glycemic control does not reduce cardiovascular events in patients with diabetes mellitus.
- Recent studies indicate that statin use may be associated with the development of diabetes mellitus; however, the overall excess risk is low.
- There is a concern that some antidiabetes agents may impart greater cardiovascular risk but there is no sufficient evidence to support one drug or combination of drugs over another for the reduction of cardiovascular events.
- Optimal medical therapy is an appropriate initial strategy in patients with diabetes mellitus, mild symptoms and moderate coronary artery disease.
- Bypass surgery is superior to percutaneous intervention in most diabetic patients with multivessel coronary disease; however, selection of the optimal myocardial revascularization strategy must take into account multiple factors and requires a multidisciplinary team approach ('heart team').

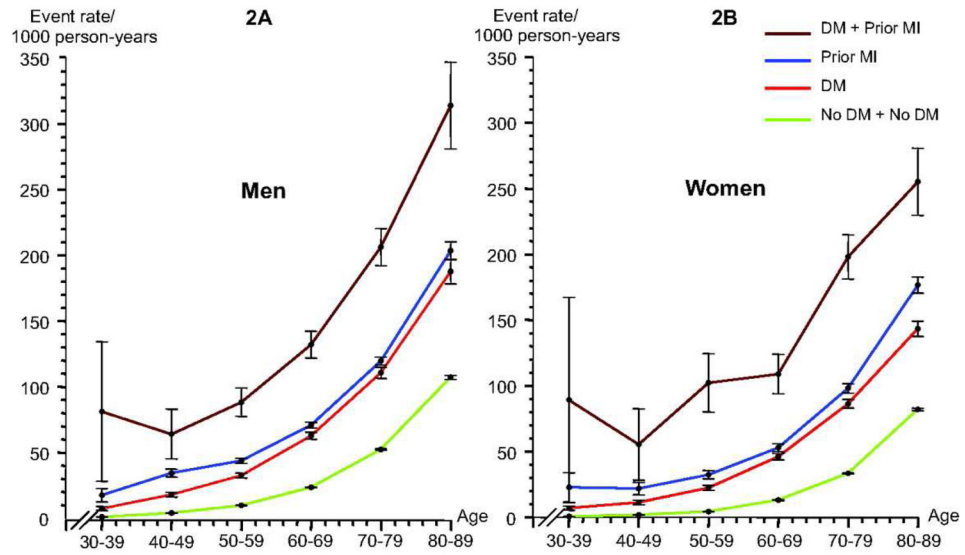


Figure 1.

Event rates for the composite endpoint of MI (nonfatal), stroke (nonfatal), and cardiovascular death in men (A) and women (B) stratified by age in relation to diabetes mellitus (DM) and a prior MI. From Schramm TK, Gislason GH, Kober L, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. *Circulation*. 2008;117:1945–1954; with permission.

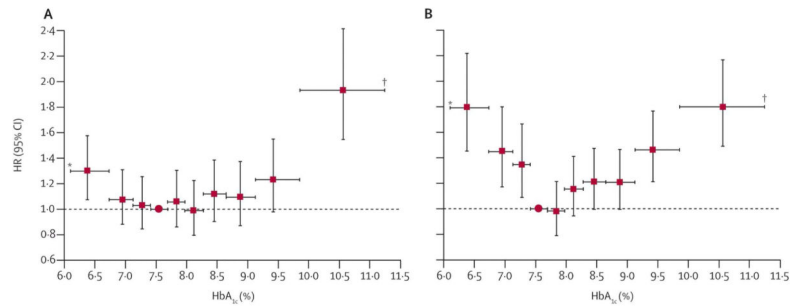


Figure 2.

Adjusted hazard ratios for all-cause mortality by HbA1c deciles in people given oral combination and insulin-based therapies. Vertical error bars show 95% CIs, horizontal bars show HbA1c range. Red circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Metformin plus sulphonylureas (A); and insulin-based regimens (B). From Currie CJ, Peters JR, Tynan A, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. *Lancet*. 2010;375:481–489; with permission.

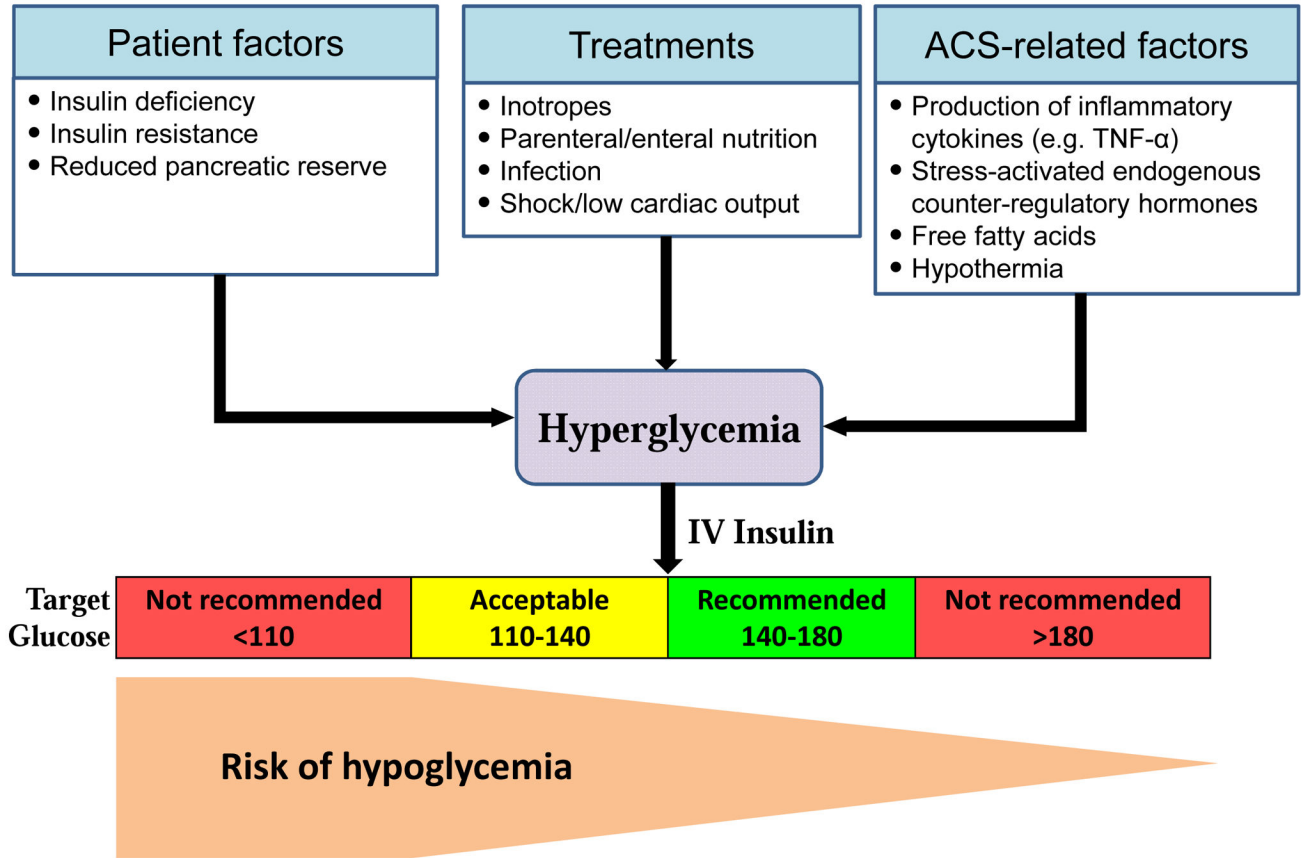


Figure 3. Management of hyperglycemia in patients with acute coronary syndromes. Adapted from Aronson D, Edelman ER. Role of CABG in the management of obstructive coronary arterial disease in patients with diabetes mellitus. *Current opinion in pharmacology.* 2012;12:134–141; with permission.

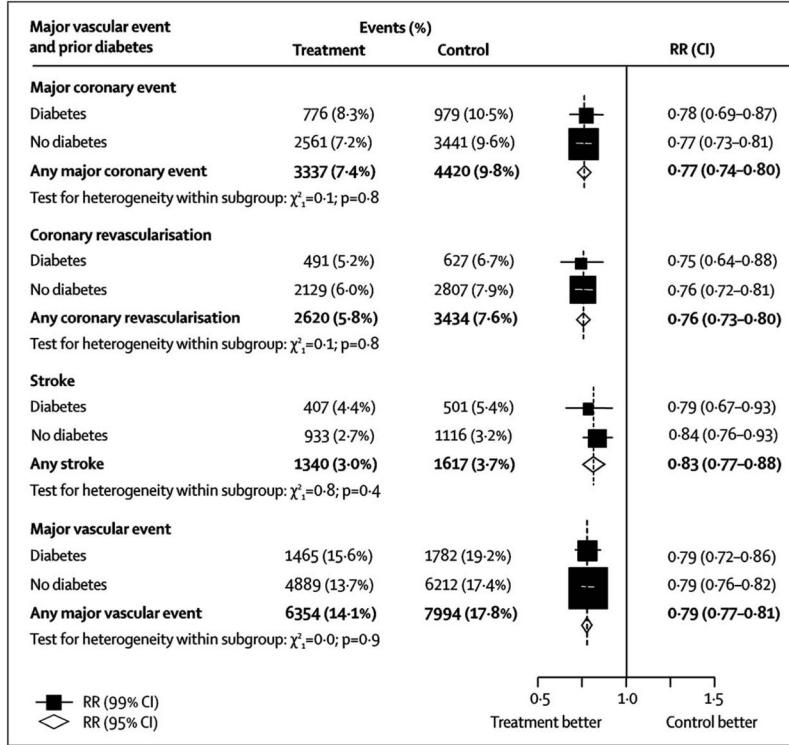


Figure 4. Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis showing proportional effects of statins on major vascular events per mmol/L reduction in LDL cholesterol in participants presenting with or without diabetes. From Cholesterol Treatment Trialists C, Kearney PM, Blackwell L, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*. 2008;371:117-125; with permission.

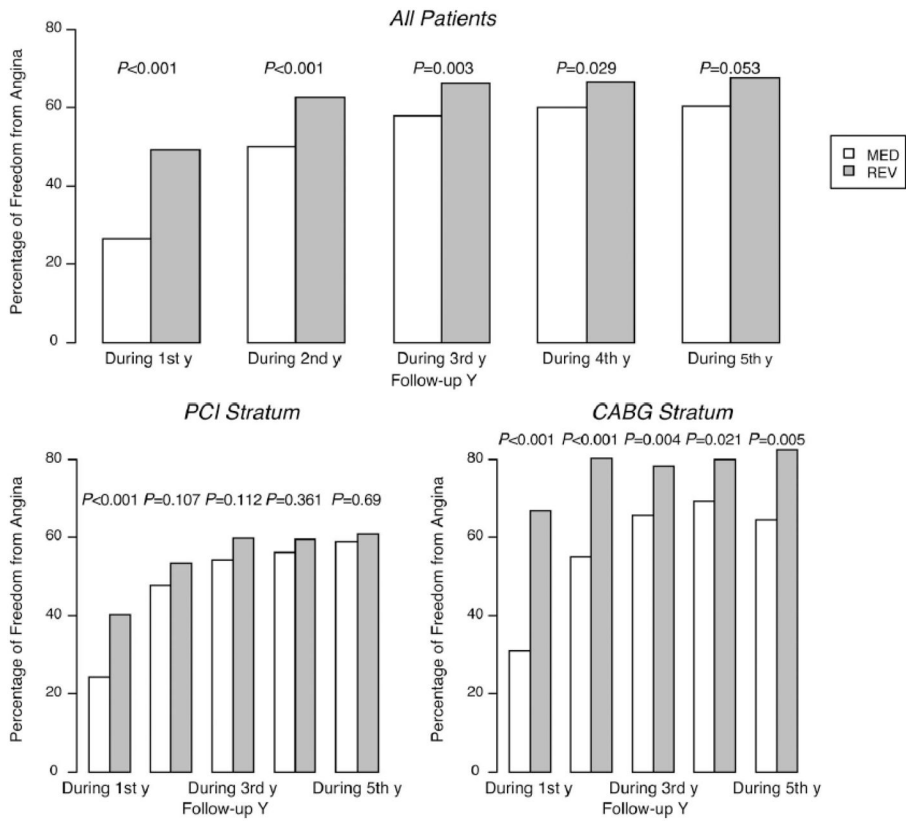


Figure 5. Annual occurrence of freedom from angina in 1434 patients with angina at entry in BARI-2D. In the PCI stratum, the increase in freedom from angina was documented only at the first year of the follow-up. In the CABG stratum, the freedom from angina was increased during the 5-year follow-up. From Dagenais GR, Lu J, Faxon DP, et al. Effects of optimal medical treatment with or without coronary revascularization on angina and subsequent revascularizations in patients with type 2 diabetes mellitus and stable ischemic heart disease. *Circulation*. 2011;123:1492–1500; with permission.

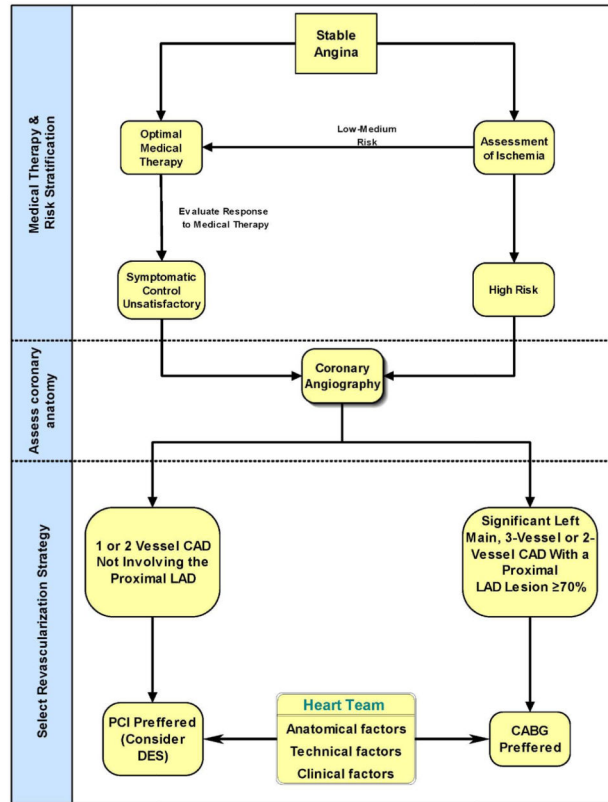


Figure 6. Revascularization strategy in patients with DM and stable angina.
* may be useful to exclude significant CAD

Table 1

Effect of antidiabetic agents on the cardiovascular system

Therapeutic classes	Effects on CVD Risk Factors	Other direct and indirect effects on the heart
Biguanides (Metformin)	Reduction in macrovascular endpoints ¹¹⁰ Improved lipid profile	—
Sulfonylureas	Weight gain	Hypoglycemia Impaired ischemic pre- conditioning ¹¹¹
Prandial glucose regulators (meglitinides)	Weight gain	Hypoglycemia
Thiazolidinediones / Glitazones	Increase LDL levels ^{20,112} Reduced restenosis after coronary stenting ^{113,114}	Heart failure ^{115,116} Excess ischemic cardiovascular risk with rosiglitazone (?) ^{23,24}
Alpha-glucosidase inhibitors	Reduced inflammatory markers ¹¹² Possible decrease in risk of cardiovascular disease event ¹¹⁷	—
DPP-4 inhibitors (gliptins)		Heart failure ^{30,116}
Amylin analogues (Pramlintide)	Weight loss	—
Incretin mimetics (GLP-1 analogues)	Weight loss	—
Insulin	Weight gain ¹¹⁸	Hypoglycemia

Data from Refs 20,32,112,116,119.

Table 2

Recommendations for Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults *with Diabetes*—Statin Treatment

Recommendations	NHLBI Grade	ACC/AHA COR	ACC/AHA LOE
Moderate-intensity statin [†] therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus.	A (Strong)	I	A
High-intensity statin [‡] therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year CVD risk unless contraindicated.	E (Expert Opinion)	Ia	B
In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for CVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy	E (Expert Opinion)	Ia	C

[†]Daily dose lowers LDL-C on average, by approximately 30% to <50% (e.g. atorvastatin 10 mg, rosuvastatin 10 mg, simvastatin 20–40 mg and pravastatin 40 mg).

[‡]Daily dose lowers LDL-C on average, by approximately 50% (e. g. atorvastatin 40–80 mg or rosuvastatin 20–40 mg).

Adapted from Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013; with permission.