Coronary Artery Disease and Diabetes Mellitus

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KEYWORDS

• Blood glucose • Coronary disease • Diabetes mellitus • Hypoglycemic agents • Revascularization • Statins

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").

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 synergistic (**Fig. 1**).[3] In addition, DM (especially type 2 DM), is associated with clustered risk factors for cardiovascular disease (CVD). Among adults with DM there is a prevalence of 75% to 85% of hypertension, 70% to 80% for elevated low-density lipoprotein (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 twofold to fourfold increased mortality risk from heart disease. More than 70% of people older than 65 years 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 approximately 25% of patients undergoing coronary artery bypass graft (CABG) surgery have DM[5]; 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 restenosis[8] and stent thrombosis.[9] Although there has been considerable improvement in the management of patients with CAD, coronary event rates remain

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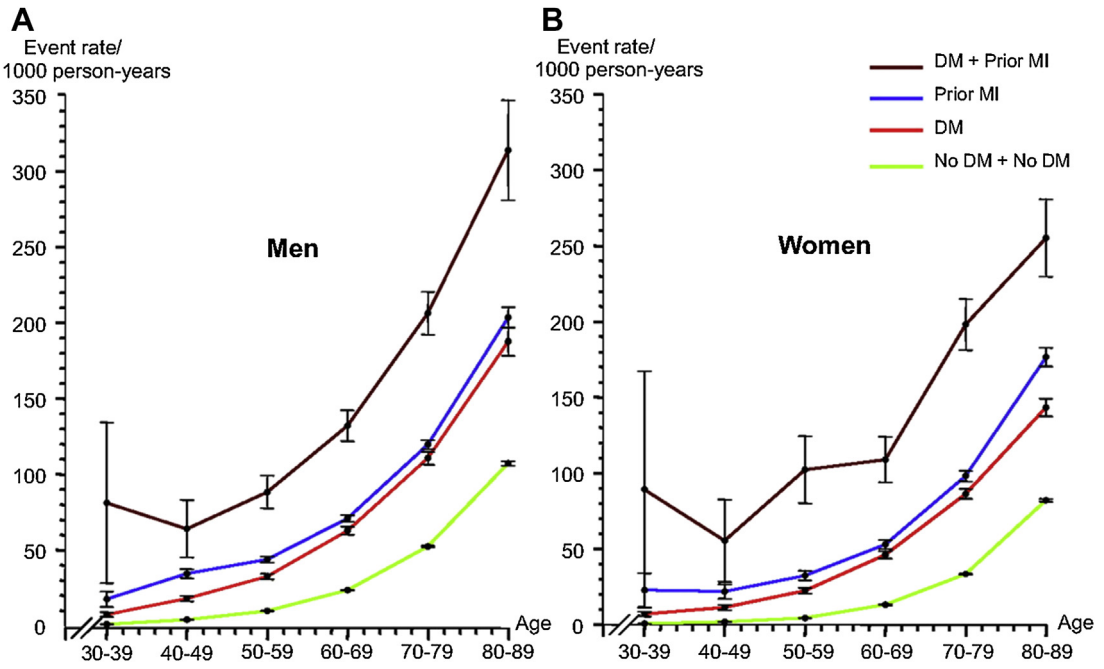

Fig. 1. Event rates for the composite endpoint of MI (nonfatal), stroke (nonfatal), and cardiovascular death in men (*A*) and women (*B*), stratified by age in relation to DM and a prior MI. (*From* Schramm TK, Gislason GH, Kober L, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. Circulation 2008;117:1945–54; with permission.)

heightened among patients with DM.[2,10–12] Therefore, optimal medical therapy (OMT) and appropriate selection of myocardial revascularization strategy are critical for patients with DM. This 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 although it has been known since antiquity, the disease we refer to can be dated only to the era after the widespread use of insulin. Before 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 life-saving 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 10,000 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 a hemoglobin (Hb) A1c lower than 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 gliclizide 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 (hazard ratio [HR] 0.90; 95% confidence interval [CI] 0.82–0.98; $P = .01$), primarily as a consequence