The prevalence of diabetes mellitus, primarily type 2 diabetes mellitus, is increasing at epidemic rates in the United States and worldwide, driven largely by increasing rates of obesity and advancing age for populations living in westernized countries. Diabetes mellitus is associated with a 2- to 4-fold increase in the risk of coronary heart disease, and among people with diabetes, about two thirds of deaths are due to cardiovascular disease, including ischemic heart disease, congestive heart failure, and stroke.1 The increase in mortality for patients with diabetes mellitus after myocardial infarction is seen both acutely and in a sustained manner and holds true for both men and women. Indeed, many have suggested diabetes mellitus to be a coronary heart disease risk equivalent, because multiple studies have demonstrated that patients with diabetes but without prior cardiovascular disease have the same event rates as individuals without diabetes but with prior cardiovascular disease.2,3 However, this suggestion has remained somewhat controversial, especially for patients at younger ages.2,4,5

Thus, to address whether diabetes mellitus accelerates the atherosclerotic process to such an extent that the presence of diabetes confers the same excess risk as that associated with prior myocardial infarction for the patient without diabetes, Schramm and colleagues,6 in the current issue of Circulation, report on the aggregate experience from the country of Denmark. All inhabitants of Denmark could be assessed with patient-level information through the Danish Civil Registration system, prescription drug use could be determined using The Danish Registry of Medicinal Product Statistics, and deaths could be identified via the Central Population Register. Integration of information from these administrative healthcare registries, together with uniform access of the population to health care, provides a definitive assessment of clinically significant risk. Furthermore, in a very large and complete population-based sample, the authors assessed important covariates in areas of previous uncertainty such as age, sex, and diabetes type. Schramm and colleagues provide definitive evidence that patients with diabetes mellitus requiring glucose-lowering therapy have cardiovascular risk comparable to nondiabetic patients with a prior myocardial infarction, regardless of age and type of diabetes.

The study design used by Schramm and colleagues6 is particularly important for its ability to address the questions on age. Studies that evaluate only older populations may have a survival bias, introduced if more severe cardiovascular disease in patients with diabetes mellitus leads to death before they are included in the study. Inclusion of all persons >30 years of age in the current report minimizes survival bias, especially in patients with type 2 diabetes mellitus. Furthermore, the clear demonstration of an increase in cardiovascular risk in younger patients with diabetes mellitus provides the clinical opportunity to administer appropriate aggressive medical therapies to prevent the evolution of future cardiovascular disease and clinical events.

Notwithstanding the great strengths of the analysis of Schramm and colleagues,6 there remain a few limitations based on the methodologies. Only individuals claiming at least 1 prescription of glucose-lowering medication in the 6-month window preceding the initiation of the observation period were classified as diabetic. All others, including those initiating glucose-lowering agents during the follow-up period, were considered referent. This definition would underestimate the persons with diabetes mellitus at the initiation of the observation period and potentially attribute diabetes risk to the referent group, thereby overestimating risk in the referent population and reducing the magnitude of the absolute and relative risk for the patients with diabetes mellitus. Onset of type 2 diabetes mellitus is difficult to date, and many persons have elevated blood glucose but do not carry the diagnosis or receive prescription medication to treat their condition. In the United States, as many as 1 of every 2 patients with type 2 diabetes mellitus may be undiagnosed. This bias might have been minimized by more broadly classifying persons as having diabetes on the basis of diagnosis by a physician, documented hyperglycemia, or both in combination, on more than 1 occasion; both are standard for the International Classification of Diseases (ICD) coding system. Exclusion of new users of antidiabetic medications from the referent group would have also reduced the rate of inappropriate group assignment. Inclusion of patients with diabetes mellitus in the referent group most likely underestimated the risk difference, which was found to be substantial despite this classification system.

Furthermore, it has been suggested that patients with diabetes mellitus are more prone to silent myocardial infarction or atypical anginal symptoms than patients without diabetes mellitus.7 This could lead to potential bias due to...
differences in detection of the cardiovascular events. Reduced event detection in the group with diabetes mellitus would likewise underestimate absolute or relative risk. However, medically undetected events could be considered less serious, or alternatively, these undiagnosed myocardial events might be anticipated to be detected by a disproportionately increased rate of ischemic heart death or all cause mortality, which Schramm and colleagues did not observe.

Effects of Diabetes Treatment on Cardiovascular Risk

The safety of the drugs available to reduce glycemia might have a profound impact on the interaction between diabetes mellitus and cardiovascular disease. Thus, it is interesting to speculate on the potential impact of cardiotoxicity of drugs used to treat diabetes mellitus. The University Group Diabetes Program found that in patients with type 2 diabetes mellitus, oral sulfonylurea therapy was associated with an increased rate of death from cardiovascular causes compared with only dietary treatment. This increase may have been due to inhibition of ischemic preconditioning by early sulfonylurea agents, a protective mechanism that reduces myocardial damage after temporary blockage of coronary blood flow. Altered ischemic preconditioning has not been seen with the newer sulfonylurea class agents. Likewise, data from an observational study that used information from a large US insurer suggested monotherapy with sulfonylurea was associated with greater risk of composite cardiovascular outcomes when compared to metformin. However, the United Kingdom Prospective Diabetes Study does not support increased cardiotoxicity in persons with type 2 diabetes mellitus randomized to sulfonylurea agents compared with those assigned to conventional therapy. Similarly, studies suggested possible increased risk of myocardial infarction and cardiovascular death associated with the thiazolidinedione rosiglitazone compared with neutral or beneficial effects demonstrated in high-risk patients with type 2 diabetes randomized to pioglitazone. Both these agents became available in Denmark only near the end of the observational time interval, and any cardiovascular effects of troglitazone remain poorly characterized. Potential effects of newer agents including incretin modulators, available only after the close of the observational window, would not affect the current findings but could have an impact on future comparative studies.

Indeed, substantial controversy exists surrounding the effects of glycemic management on cardiovascular outcomes in patients with diabetes mellitus. Despite strong associations between increasing glycemia and cardiovascular risk, it has been difficult to clearly demonstrate that lowering of blood glucose improves cardiovascular outcomes in patients with type 2 diabetes mellitus. In patients with type 1 diabetes, it took many years to demonstrate the benefits of intensive glycemic control to modestly reduce event rates. It is in this light that the very recent findings from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial are quite surprising. The complex trial design is a randomized, multicenter, double 2×2 factorial investigation evaluating the effects on major cardiovascular disease events of intensive glycemia control, of treatment to increase high-density lipoprotein cholesterol and to lower triglycerides, and of intensive blood pressure control (with both lipid and blood pressure management in the context of good glycemia control) on major cardiovascular disease events. The study involved 10,251 participants with type 2 diabetes mellitus and established heart disease or at least 2 additional risk factors, including hypertension, elevated cholesterol, obesity, and smoking. Glycemic therapeutic strategies targeted near-normal HbA1c levels of <6.0%, compared with the standard of care of 7.0% to 7.9%. A variety of US Food and Drug Administration–approved medications were used in glycemic management. The glycemic arm of the trial was stopped 18 months prematurely when excess deaths were found in the intensive treatment arm. The intensive treatment group achieved a median HbA1c of 6.4% compared with 7.5% in the standard care group. Over an average of 4 years of follow-up, 257 deaths occurred (14 deaths per 1000 persons annually) in the intensive treatment group compared with 203 deaths (11 deaths per 1000 persons annually) in the standard care group. Excess deaths do not appear to be directly attributable to hypoglycemia or to any single drug or combination of drugs. Fewer nonfatal cardiovascular events occurred in the intensive treatment group; however, mortality could be attributed to both higher rates of fatal cardiovascular events as well as to noncardiovascular causes, such as cancer. The study participants in the intensive glycemic treatment arm will now receive less-intensive standard glycemic treatment, and the lipid and blood pressure arms of the trial will continue. Perhaps intensive glycemic management plays a greater role in primary prevention of atherosclerosis compared with secondary prevention in the setting of established disease. In contrast, preliminary reports on the analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study, which involved 11,140 high-risk patients with type 2 diabetes mellitus in a 2×2 factorial design study of blood pressure lowering and intensive glucose lowering with a target HbA1c of <6.5%, do not confirm increased risk of death among the participants receiving more intensive glycemic treatment (www.advance-trial.com). While the medical community awaits the detailed analysis and full report of the ACCORD and ADVANCE findings, the need to develop and establish safe and effective treatment strategies to manage the increased cardiovascular risk in patients with diabetes mellitus is clear. Therapeutic goals must be individualized, and multifactorial interventions to reduce cardiovascular event rates must be employed.

The need for multifactorial interventions in diabetes management is enforced by the recently reported Steno-2 Study (Steno Diabetes Center, Copenhagen, Denmark). 160 patients with type 2 diabetes mellitus and microalbuminuria received conventional therapy or intensive target-driven therapy involving a combination of medication and behavior-driven interventions to reduce glycemia, cholesterol, and blood pressure, followed by an observational period. Whereas glycemic targets were aimed at HbA1c <6.5%, actual levels at the end of the mean 7.8 years of study intervention were 7.9% in the intensive group, compared with 9.0% in the
conventional arm. However, at the end of intervention, systolic blood pressure was 15 mm Hg lower, diastolic blood pressure was 5 mm Hg lower, and low-density lipoprotein cholesterol was 1.11 mmol/L (43 mg/dL) lower in the intensive treatment group compared with conventional therapy. Multifactorial interventions were shown to reduce the risk of cardiovascular and microvascular events by ≈50% and importantly to have sustained benefits with respect to vascular complications and cardiovascular and all-cause mortality.16

Glimpse of the Future
With the major finding of Schramm and colleagues6 firmly establishing that all patients >30 years of age who require glucose-lowering treatment are at particularly high risk of cardiovascular morbidity and mortality, it is time to look forward at therapeutic options to reduce this ominous risk.

Available risk calculators to accurately estimate the risk of new coronary events in people with type 2 diabetes mellitus have been developed on the basis of data from 4540 United Kingdom Prospective Diabetes Study participants.13 This diabetes-specific model incorporates glycemia, systolic blood pressure, and lipid levels as risk factors in addition to age, sex, ethnic group, smoking status, and time since diagnosis of diabetes and demonstrates that the impact of increase in lipids carries >3 times the risk contributed by the other variables. This disparity suggests that whereas smoking cessation and blood pressure and glycemic control are meaningful in the patient with diabetes mellitus, modification of lipid profiles is of primary importance and worth special attention.

Clinical trial evidence supports the value of lipid-lowering therapy for patients with diabetes mellitus, and statins have been a medical breakthrough to achieve this aim and provide effective primary and secondary cardiovascular protection. The Heart Protection Study (HPS), which included nearly 6000 participants with diabetes mellitus, demonstrated that cholesterol lowering with simvastatin reduced the rate of first major vascular events by >25%, even in patients without established coronary disease or markedly elevated baseline cholesterol levels.17 The landmark Collaborative Atorvastatin Diabetes (CARDS) Study18 demonstrated that treatment with atorvastatin, 10 mg daily, compared with placebo resulted in a 37% reduction in major cardiovascular events in type 2 diabetic patients with low-density lipoprotein cholesterol levels 4.14 mmol/L (160 mg/dL) or lower over a mean follow-up of 4 years. The recent meta-analysis of 14 randomized trials of statins includes 18 686 patients with diabetes mellitus, consisting of 1466 with type 1 and 17 220 with type 2 diabetes mellitus. It demonstrated a 9% proportional reduction in all-cause mortality for each mmol/L reduction in low-density lipoprotein cholesterol over a mean follow-up of 4.3 years.19 In addition, reductions occurred in myocardial infarction, coronary death, coronary revascularization, and stroke (Hazard Ratio ranging from 0.75 to 0.79, all significant). The proportional effects of statin administration were seen in patients with diabetes mellitus regardless of whether or not they had a prior history of vascular disease and irrespective of other baseline characteristics.

Recent rigorous clinical investigations support markedly lower cholesterol targets then previously considered to be warranted. Among patients with coronary heart disease who have low low-density lipoprotein cholesterol, those with diabetes mellitus have increased event rates compared to those without diabetes mellitus. Importantly, statin therapy can reduce the event rates in the patients with diabetes mellitus to those of the nondiabetic population.20 In Denmark, at the time of the initiation of the studies to assess cardiovascular risk by Schramm and colleagues,6 statin use was under 12% in men and women with diabetes and prior myocardial infarction and under 2% for patients with diabetes and no prior infarct.

In conclusion, it can only be hoped that through recognition of the clear cardiovascular risk associated with diabetes mellitus, interventions for both primary and secondary cardiovascular disease prevention will gain widespread clinical application and new standards of care will reduce cardiovascular morbidity and mortality in patients with and without diabetes alike. Meanwhile, optimal targets for glycemic management need to be better understood and safe and effective therapeutics developed in order to conquer this disease.

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