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Why are we doing cardiovascular outcome trials in type 2 diabetes?

ABSTRACT

Cardiovascular disease is the leading cause of morbidity and death in people with diabetes mellitus. While worsening hyperglycemia is directly associated with poorer outcomes, studies aiming at euglycemia have failed to show an advantage over modest glucose-lowering strategies. Several diabetes drugs that were approved solely on the basis of their glucose-lowering potential were later shown to increase cardiovascular risk.

KEY POINTS

The worldwide burden of type 2 diabetes is increasing dramatically as obesity rates increase, populations age, and people around the world adopt a Western diet.

Diabetes increases the risk of atherosclerotic cardiovascular disease, which remains the leading cause of death in diabetic patients.

Lowering blood glucose alone may not necessarily amount to reduction in adverse cardiovascular events.

Clinical trials of new drugs for type 2 diabetes must prove cardiovascular safety in addition to glucose-lowering potential before the drugs gain final regulatory approval.

Aggressive risk factor modification (smoking cessation, control of hypertension, and treatment of hyperlipidemia with statins) remains paramount in reducing cardiovascular risk in people with diabetes.

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A 50-year-old man with hypertension presents to the internal medicine clinic. He has been an active smoker for 15 years and smokes 1 pack of cigarettes a day. He was recently diagnosed with type 2 diabetes mellitus after routine blood work revealed his hemoglobin A_{1c} level was elevated at 7.5%. He has no current complaints but is concerned about his future risk of a heart attack or stroke.

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THE BURDEN OF DIABETES MELLITUS

The prevalence of diabetes mellitus in US adults (age > 20) has tripled during the last 30 years to 28.9 million, or 12% of the population in this age group.[1] Globally, 382 million people had a diagnosis of diabetes in 2013, and with the increasing prevalence of obesity and adoption of a Western diet, this number is expected to escalate to 592 million by 2035.[2]

HOW GREAT IS THE CARDIOVASCULAR RISK IN PEOPLE WITH DIABETES?

Diabetes mellitus is linked to a twofold increase in the risk of adverse cardiovascular events even after adjusting for risk from hypertension and smoking.[3] In early studies, diabetic people with no history of myocardial infarction were shown to have a lifetime risk of infarction similar to that in nondiabetic people who had already had an infarction,[4] thus establishing diabetes as a "coronary artery disease equivalent." Middle-aged men diagnosed with diabetes lose an average of 6 years of life and women lose 7 years compared with those without diabetes, with cardiovascular morbidity contributing to more than half of this reduction in life expectancy (**FIGURE 1**).[5]

Trials discussed in this article

ACCORD—Action to Control Cardiovascular Risk in Diabetes[9]

ADVANCE—Action in Diabetes and Vascular Disease[8]

BARI-2D—Bypass Angioplasty Revascularization Investigation 2 DM[30]

CARDS—Collaborative Atorvastatin Diabetes Study[15]

DIAD—Detection of Anemia in Asymptomatic Diabetics[26]

EXAMINE—Examination of Cardiovascular Outcomes Study of Alogliptin Versus Standard of Care[34]

FREEDOM—Future Revascularization Evaluation in Patients With DM: Optimal Management of Multivessel Disease[29]

SAVOR—Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With DM (SAVOR–TIMI 53)[35]

UKPDS—United Kingdom Prospective Diabetes Study[7]

VADT—The Veterans Affairs Diabetes Trial[10]

Numerous mechanisms have been hypothesized to account for the association between diabetes and cardiovascular risk, including increased inflammation, endothelial and platelet dysfunction, and autonomic dysregulation.[6]

Diabetes is a coronary artery disease equivalent for risk of death

Can we modify cardiovascular risk in patients with diabetes?

Although fasting blood glucose levels strongly correlate with future cardiovascular risk, whether lowering blood glucose levels with medications will reduce cardiovascular risk has been uncertain.[3] Lowering glucose beyond what is current standard practice has not been shown to significantly improve cardiovascular outcomes or mortality rates, and it comes at the price of an increased risk of hypoglycemic events.

No macrovascular benefit from lowering hemoglobin A_{1c} beyond the standard of care

UKPDS.[7] Launched in 1977, the United Kingdom Prospective Diabetes Study was designed to investigate whether intensive blood glucose control reduces the risk of macrovascular and microvascular complications in type 2 diabetes. The study randomized nearly 4,000 patients newly diagnosed with diabetes to intensive treatment (with a sulfonylurea or insulin to keep fasting blood glucose levels below 110 mg/dL) or to conventional treatment (with diet alone unless hyperglycemic symptoms or a fasting blood glucose more than 270 mg/dL arose) for 10 years.

Multivariate analysis from the overall study population revealed a direct correlation between hemoglobin A_{1c} levels and adverse cardiovascular events. Higher hemoglobin A_{1c} was associated with markedly more:

- Fatal and nonfatal myocardial infarctions (14% increased risk for every 1% rise in hemoglobin A_{1c})
- Fatal and nonfatal strokes (12% increased risk per 1% rise in hemoglobin A_{1c})
- Amputations or deaths from peripheral vascular disease (43% increase per 1% rise)
- Heart failure (16% increase per 1% rise).

While intensive therapy was associated with significant reductions in microvascular events (retinopathy and proteinuria), there was no significant difference in the incidence of major macrovascular events (myocardial infarction or stroke).

The mean hemoglobin A_{1c} level at the end of the study was about 8% in the standard-treatment group and about 7% in the intensive-treatment group. Were these levels low enough to yield a significant risk reduction? Since lower hemoglobin A_{1c} levels are associated with lower risk of myocardial infarction, it seemed reasonable to do further studies with more intensive treatment to further lower hemoglobin A_{1c} goals.

ADVANCE.[8] The Action in Diabetes and Vascular Disease trial randomized more than 11,000 participants with type 2 diabetes to either usual care or intensive therapy with a goal of achieving a hemoglobin A_{1c} of 6.5% or less. During 5 years of follow-up, the usual-care group averaged a hemoglobin A_{1c} of 7.3%, compared with 6.5% in the intensive-treatment group.

No significant differences between the two groups were observed in the incidence of major macrovascular events, including myocardial infarction, stroke, or death from any cause. The intensive-treatment group had fewer major microvascular events, with most of the benefit being in the form of a lower incidence of proteinuria, and with no significant effect on retinopathy. Severe hypoglycemia, although uncommon, was more frequent in the intensive-treatment group.

Estimated future years of life lost owing to diabetes

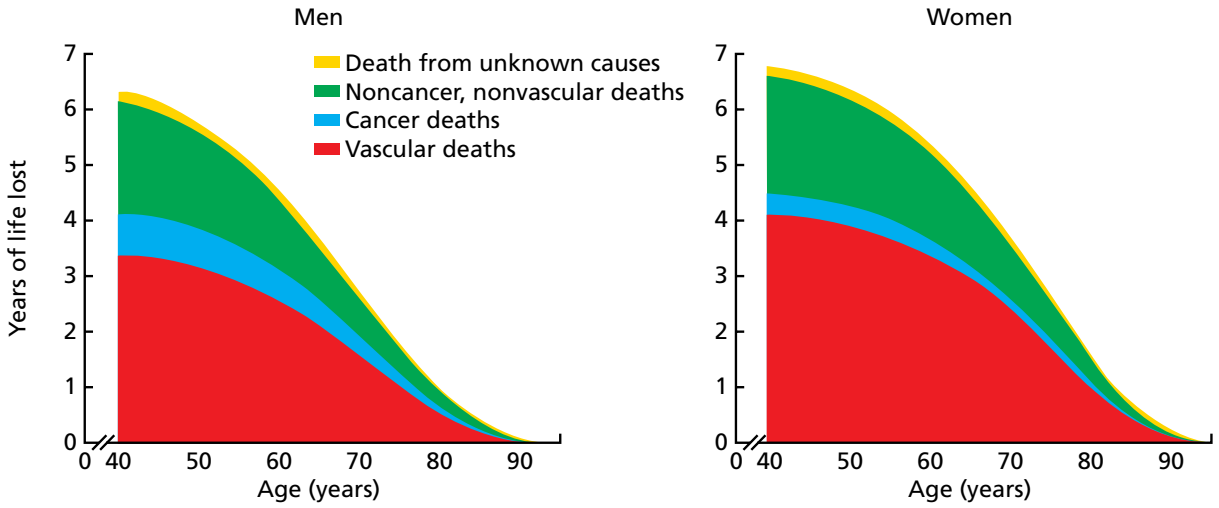

FIGURE 1. The Emerging Risk Factors Collaboration found that 50-year-old people with diabetes died an average of 6 years sooner than their counterparts without diabetes. People with known preexisting cardiovascular disease at baseline were excluded from the analysis shown here.

ACCORD.[9] The Action to Control Cardiovascular Risk in Diabetes trial went one step further. This trial randomized more than 10,000 patients with type 2 diabetes to receive either intensive therapy (targeting hemoglobin $A_{1c} \leq 6.0\%$) or standard therapy (hemoglobin A_{1c} 7.0%–7.9%). At 1 year, the mean hemoglobin A_{1c} levels were stable at 6.4% in the intensive-therapy group and 7.5% in the standard-therapy group.

The trial was stopped at 3.5 years because of a higher rate of death in the intensive-therapy group, with a hazard ratio of 1.22, predominantly from an increase in adverse cardiovascular events. The intensive-therapy group also had a significantly higher incidence of hypoglycemia.

VADT.[10] The Veterans Affairs Diabetes Trial randomized 1,791 patients with type 2 diabetes who had a suboptimal response to conventional therapy to receive intensive therapy aimed at reducing hemoglobin A_{1c} by 1.5 percentage points or standard therapy. After a follow-up of 5.6 years, median hemoglobin A_{1c} levels were 8.4% in the standard-therapy group and 6.9% in the intensive-therapy group. No differences were found between the two groups in the incidence of major cardiovascular events, death, or microvascular complications, with the exception of a lower rate of progression of albuminuria in the intensive-therapy group. The rates of adverse events, primarily hypoglycemia, were higher in the intensive-therapy group.

Based on these negative trials and concern about potential harm with intensive glucose-lowering strategies, standard guidelines continue to recommend moderate glucose-lowering strategies for patients with diabetes. The guidelines broadly recommend targeting a hemoglobin A_{1c} of 7% or less while advocating a less ambitious goal of lower than 7.5% or 8.0% in older patients who may be prone to hypoglycemia.[11]

People with diabetes lose 6–7 years of life, mostly from cardiovascular disease

STRATEGIES TO REDUCE CARDIOVASCULAR RISK IN DIABETES

While the incidence of diabetes mellitus has risen alarmingly, the incidence of cardiovascular complications of diabetes has declined over the years. Lowering blood glucose has not been the critical factor mediating this risk reduction. In addition to smoking cessation, proven measures that clearly reduce long-term

cardiovascular risk in diabetes are blood pressure control and reduction in low-density lipoprotein cholesterol with statins.

Lower the blood pressure to less than 140 mm Hg

ADVANCE.[12] In the ADVANCE trial, in addition to being randomized to usual vs intensive glucose-lowering therapy, participants were also simultaneously randomized to receive either placebo or the combination of an angiotensin-converting enzyme inhibitor and a diuretic (ie, perindopril and indapamide). Blood pressure was reduced by a mean of 5.6 mm Hg systolic and 2.2 mm Hg diastolic in the active-treatment group. This moderate reduction in blood pressure was associated with an 18% relative risk reduction in death from cardiovascular disease and a 14% relative risk reduction in death from any cause.

The ACCORD trial[13] lowered systolic blood pressure even more in the intensive-treatment group, with a target systolic blood pressure of less than 120 mm Hg compared with less than 140 mm Hg in the control group. Intensive therapy did not prove to significantly reduce the risk of major cardiovascular events and was associated with a significantly higher rate of serious adverse events.

Therefore, while antihypertensive therapy lowered the mortality rate in diabetic patients, lowering blood pressure beyond conventional blood pressure targets did not decrease the risk more. The latest hypertension treatment guidelines (from the eighth Joint National Committee) emphasize a blood pressure goal of 140/90 mm Hg or less in adults with diabetes.[14]

The role of aspirin in patients with diabetes remains controversial

Prescribe a statin regardless of the baseline lipid level

The Collaborative Atorvastatin Diabetes Study (CARDS) randomized nearly 3,000 patients with type 2 diabetes mellitus and no history of cardiovascular disease to either atorvastatin 10 mg or placebo regardless of cholesterol status. The trial was terminated 2 years early because a prespecified efficacy end point had already been met: the treatment group experienced a markedly lower incidence of major cardiovascular events, including stroke.[15]

A large meta-analysis of randomized trials of statins noted a 9% reduction in all-cause mortality (relative risk [RR] 0.91, 99% confidence interval 0.82–1.01; $P = .02$) per mmol/L reduction in low-density lipoprotein cholesterol in patients with diabetes mellitus.[16] Use of statins also led to significant reductions in rates of major coronary events (RR 0.78), coronary revascularization (RR 0.75), and stroke (RR 0.79).

The latest American College of Cardiology/American Heart Association guidelines endorse moderate-intensity or high-intensity statin treatment in patients with diabetes who are over age 40.[17]

Encourage smoking cessation

Smoking increases the lifetime risk of developing type 2 diabetes.[18] It is also associated with premature development of microvascular and macrovascular complications of diabetes,[19] and it leads to increased mortality risk in people with diabetes mellitus in a dose-dependent manner.[20] Therefore, smoking cessation remains paramount in reducing cardiovascular risk, and patients should be encouraged to quit as soon as possible.

Role of antiplatelet agents

Use of antiplatelet drugs such as aspirin for primary prevention of cardiovascular disease in patients with diabetes is controversial. Initial studies showed a potential reduction in the incidence of myocardial infarction in men and stroke in women with diabetes with low-dose aspirin.[21,22] Subsequent randomized trials and meta-analyses, however, yielded contrasting results, showing no benefit in cardiovascular risk reduction and potential risk of bleeding and other gastrointestinal adverse effects.[23,24]

The US Food and Drug Administration (FDA) has not approved aspirin for primary prevention of cardiovascular disease in people who have no history of cardiovascular disease. In contrast, the American Heart Association and the American Diabetes Association endorse low-dose aspirin (75–162 mg/day) for adults with diabetes and no history of vascular disease who are at increased cardiovascular risk (estimated 10-year risk of events > 10%) and who are not at increased risk of bleeding.

In the absence of a clear consensus and given the lack of randomized data, the role of aspirin in patients with diabetes remains controversial.

WHAT IS THE ROLE OF STRESS TESTING IN ASYMPTOMATIC DIABETIC PATIENTS?

People with diabetes also have a high incidence of silent (asymptomatic) ischemia that potentially leads to worse outcomes.[25] Whether screening for silent ischemia improves outcomes in these patients is debatable.

The Detection of Anemia in Asymptomatic Diabetics (DIAD) trial randomized more than 1,000 asymptomatic diabetic participants to either screening for coronary artery disease with stress testing or no screening.[26] Over a 5-year follow-up, there was no significant difference in the incidence of myocardial infarction and death from cardiac causes.

The guidelines remain divided on this clinical conundrum. While the American Diabetes Association recommends against routine screening for coronary artery disease in asymptomatic patients with diabetes, the American College of Cardiology/American Heart Association guidelines recommend screening with radionuclide imaging in patients with diabetes and a high risk of coronary artery disease.[27]

ROLE OF REVASCULARIZATION IN DIABETIC PATIENTS WITH STABLE CORONARY ARTERY DISEASE

Patients with coronary artery disease and diabetes fare worse than those without diabetes, despite revascularization by coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).[28]

The choice of CABG or PCI as the preferred revascularization strategy was recently studied in the Future Revascularization Evaluation in Patients With DM: Optimal Management of Multivessel Disease (FREEDOM) trial.[29] This study randomized 1,900 patients with diabetes and multivessel coronary artery disease to revascularization with PCI or CABG. After 5 years, there was a significantly lower rate of death and myocardial infarction with CABG than with PCI.

The role of revascularization in patients with diabetes and stable coronary artery disease has also been questioned. The Bypass Angioplasty Revascularization Investigation 2 DM (BARI-2D) randomized 2,368 patients with diabetes and stable coronary artery disease to undergo revascularization (PCI or CABG) or to receive intensive medical therapy alone.[30] At 5 years, there was no significant difference in the rates of death and major cardiovascular events between patients undergoing revascularization and those undergoing medical therapy alone. Subgroup analysis revealed a potential benefit with CABG over medical therapy in patients with more extensive coronary artery disease.[31]

CAN DIABETES THERAPY CAUSE HARM?

New diabetes drugs must show no cardiovascular harm

Several drugs that were approved purely on the basis of their potential to reduce blood glucose were reevaluated for impact on adverse cardiovascular outcomes.

Muraglitazar is a peroxisome proliferator-activated receptor agonist that was shown in phase 2 and 3 studies to dramatically lower triglyceride levels in a dose-dependent fashion while raising high-density lipoprotein levels and being neutral to low-density lipoprotein levels. It also lowers blood glucose. The FDA Advisory Committee voted to approve its use for type 2 diabetes based on phase 2 trial data. But soon after, a meta-analysis revealed that the drug was associated with more than twice the incidence of cardiovascular complications and death than standard therapy.[32] Further development of this drug subsequently ceased.

New drugs must not only lower blood sugar, they also must not increase cardiovascular risk

A similar meta-analysis was performed on rosiglitazone, a drug that has been available since 1997 and had been used by millions of patients. Rosiglitazone was also found to be associated with a significantly increased risk of cardiovascular death, as well as death from all causes.[33]

In light of these findings, the FDA in 2008 issued new guidelines to the diabetes drug development industry. Henceforth, new diabetes drugs must not only lower blood glucose, they must also be shown in a large clinical trial not to increase cardiovascular risk.

Current trials will provide critical information

Numerous trials are now under way to assess cardiovascular outcomes with promising new diabetes drugs. Tens of thousands of patients are involved in trials testing dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 agonists, sodium-glucose-linked transporter-2 agents, and a GPR40 agonist.

Because of the change in guidelines, results over the next decade should reveal much more about the impact of lowering blood glucose on heart disease than we learned in the previous century.

Two apparently neutral but clinically relevant trials recently examined cardiovascular outcomes associated with diabetes drugs.

EXAMINE.[34] The Examination of Cardiovascular Outcomes Study of Alogliptin Versus Standard of Care study randomized 5,380 patients with type 2 diabetes and a recent acute coronary syndrome event (acute myocardial infarction or unstable angina requiring hospitalization) to receive either alogliptin (a DPP-4 inhibitor) or placebo in addition to existing standard diabetes and cardiovascular therapy. Patients were followed for up to 40 months (median 18 months). Hemoglobin A_{1c} levels were significantly lower with alogliptin than with placebo, but the time to the primary end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was not significantly different between the two groups.

SAVOR.[35] The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with DM (SAVOR–TIMI 53) trial randomized more than 16,000 patients with established cardiovascular disease or multiple risk factors to either the DPP-4 inhibitor saxagliptin or placebo. The patients' physicians were permitted to adjust all other medications, including standard diabetes medications. The median treatment period was just over 2 years. Similar to EXAMINE, this study found no difference between the two groups in the primary end point of cardiovascular death, myocardial infarction, or ischemic stroke, even though glycemic control was better in the saxagliptin group.

Thus, both drugs were shown not to increase cardiovascular risk, an FDA criterion for drug marketing and approval.

CONTROL MODIFIABLE RISK FACTORS

There has been an alarming rise in the incidence of diabetes and obesity throughout the world. Cardiovascular disease remains the leading cause of death in patients with diabetes. While elevated blood glucose in diabetic patients leads to increased cardiovascular risk, efforts to reduce blood glucose to euglycemic levels may not lead to a reduction in this risk and may even cause harm.

Success in cardiovascular risk reduction in addition to glucose-lowering remains the holy grail in the development of new diabetes drugs. But in the meantime, aggressive control of other modifiable risk factors such as hypertension, smoking, and hyperlipidemia remains critical to reducing cardiovascular risk in diabetic patients.

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