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Cardiovascular Protection in the Treatment of Type 2 Diabetes: A Review of Clinical Trial Results Across Drug Classes

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ABSTRACT

Patients with type 2 diabetes (T2DM) have a significantly higher risk of developing cardiovascular disease (CVD)—namely myocardial infarction, heart failure, and stroke. Despite clear advances in the prevention and treatment of CVD, the impact of T2DM on CVD outcome remains high and continues to escalate. Available evidence indicates that the risk of macrovascular complications increases with the severity of hyperglycemia, thus suggesting that the relation between metabolic disturbances and vascular damage is approximately linear. Although current antidiabetic drugs are highly effective for the management of hyperglycemia, most T2DM patients remain exposed to a substantial and concrete risk of CVD. Over the last decade many glucose-lowering agents have been tested for their safety and efficacy in T2DM with CVD. Noteworthy, most of these studies failed to show a significant benefit in terms of CV morbidity and mortality, despite intensive glycemic control. The recent trials Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients−Removing Excess Glucose (EMPA-REG OUTCOME); Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6); Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER); and Insulin Resistance Intervention After Stroke (IRIS) have shed some light on this important clinical issue, thus showing a convincing effect of empagliflozin, liraglutide, and pioglitazone on CVD outcomes. Here we provide a critical and updated overview of the main glucose-lowering agents and their risk/benefit ratio for the prevention of CVD in patients with T2DM.

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GLUCOSE-LOWERING STRATEGIES AND CARDIOVASCULAR DISEASE

Epidemiologic studies have outlined a strong association between type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).[1,2] It is well established that patients with T2DM are exposed to a significantly higher risk to develop myocardial infarction (MI) and stroke than matched subjects without T2DM.[2] Diabetic patients hospitalized for unstable angina or non-Q-wave MI display a significantly higher 2-year morbidity and mortality as compared with

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nondiabetic subjects.[3] In the seminal study by Haffner et al,[4] the 7-year risk of MI was as high in diabetic patients without prior MI as it was in nondiabetic patients with prior MI, thus establishing diabetes as a "CV disease risk equivalent." The increased prevalence of CVD in the setting of T2DM can be largely attributed to the heavy atherosclerotic burden and adverse plaque phenotype, as well as the inability to compensate for these alterations.[5,6]

Despite clear advances in the prevention and treatment of CVD, the impact of T2DM on CVD outcome remains significant and continues to escalate as the obesity epidemic takes its toll.[7] Even though the CVD burden has been reduced over the last decade, this is only partially true in the diabetic patient. Data accumulated over the last 10 years strongly suggest that the risk of macrovascular complications increases with the severity of abnormality of blood glucose, indicating that the relation between metabolic disturbances and vascular damage is approximately linear.[8,9] In the large, prospective Norfolk study, the relationship between glycated hemoglobin (HbA_{1c}), CVD, and total mortality was indeed linear, even among patients without T2DM; of note, 72% of the events occurred in persons with HbA_{1c} concentrations between 5% and 6.9%.[10] In other words, CVD may already be detectable in patients with HbA_{1c} values below the diagnostic threshold for diabetes, whereas in patients with overt T2DM the relative risk of CVD has been shown to increase by approximately 16% for every percentage point increase in HbA_{1c}.[10]

Given this background, one can certainly postulate that—similar to hypertension and hypercholesterolemia—approaches aiming at reducing the hyperglycemic burden should result in a clear-cut reduction of vascular events in the diabetic population. However, the relation between glucose-lowering approaches and CVD is much more complex than is the case with other cardiovascular (CV) risk factors. Indeed, the success of glucose-lowering strategies in terms of CV outcome cannot be easily predicted from changes in surrogate endpoints (such as plasma glucose levels or HbA_{1c}).[6] Although HbA_{1c} is a reliable marker of glycemic control, it may explain less than 25% of the risk of developing diabetic microvascular complications.[11] This may be partially explained by the notion that HbA_{1c} does not correlate with glycemic variability when adjusted for mean blood glucose, and tailoring glucose-lowering strategies only on the level of HbA_{1c} may leave diabetic patients exposed to a substantial burden of glycemic peaks and nadirs.[12] Despite the increasing number of individuals affected by T2DM, few definitive CV outcome trials of licensed therapies have been performed.[13-15] In the present review we critically discuss the effects of different glucose-lowering medications on CVD outcomes (**Table 1**) in patients with T2DM.

METFORMIN

Metformin—a biguanide that reduces hepatic glucose production while improving insulin sensitivity—is still considered the first-line drug for the treatment of T2DM patients.[16] This is mostly due to the fact that metformin is overall well tolerated, effectively lowers HbA_{1c} levels by 1% to 2%, has a favorable impact on body weight, does not increase the risk of hypoglycemia when given in monotherapy, and last but not least, is highly cost-effective.[16] Of note, metformin is one of the few drugs showing a significant reduction of macrovascular events and diabetes-related mortality. Cardiovascular benefits of metformin mostly derive from the UK Prospective Diabetes Study (UKPDS) trial, the results of which were published in 1998.[17] In this trial 3867 patients with newly diagnosed T2DM were randomized to intensive treatment with sulfonylureas or with insulin, versus conventional therapy.[17] A subgroup of UKPDS patients who were overweight (>120% ideal body weight) were randomized either to intensive therapy with metformin (n = 342) or conventional dietary measures (n = 411).[17] In this group of patients, treatment with metformin was associated with a 32% reduction of any diabetes-related endpoint ($P = .002$), 42% reduction in diabetes-related death ($P = .017$), and 36% reduction in mortality ($P = .011$). Most interestingly from a CV perspective, patients receiving metformin displayed a 39% reduction in the risk of nonfatal MI ($P = .01$).[17] Despite the small number of patients enrolled, the protective effects of metformin were still observed in the 10-year posttrial monitoring of patients who survived to the end of the UKPDS trial.[18] Although HbA_{1c} levels were no longer different between intensive and conventional arms, metformin-related risk reductions persisted for any diabetes-related endpoint, MI (33%, $P = .005$), and mortality (27%, $P = .002$).[18] Although UKPDS provides some evidence—albeit with limited statistical power compared with other CV outcome trials—that metformin may represent a cardioprotective agent, not many randomized trials have been performed to confirm the CV benefits of the drug.[19] After the publication of the UKPDS, only 1 randomized, placebo-controlled trial was performed.[20] In this relatively small trial, 390 patients treated with insulin were randomized to either metformin or placebo. The primary endpoint was an aggregate of microvascular and macrovascular morbidity and mortality, whereas the secondary endpoint was defined by microvascular and macrovascular morbidity and mortality, as separate aggregate scores. After 4.3 years, metformin was not associated with an improvement in the primary endpoint (hazard ratio [HR] 0.92, $P = .33$), but there was a reduction in the secondary endpoint of macrovascular events (HR 0.61, $P = .02$). Moreover, metformin improved body weight and glycemic control and reduced the requirement of insulin.[20] These overall positive findings prompted the investigators to conclude that metformin treatment should be continued after the introduction of insulin in any patient with T2DM, unless contraindicated.

The remaining evidence, and perhaps the largest body of data, comes from observational studies showing that metformin use, either as monotherapy or in combination with another oral agent, has been associated with reduced CV events, CV deaths, and total mortality.[21-24] Despite the fact