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Review Article

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Paradigm Shift for the Treatment of Type 2 Diabetes Mellitus in Patients with Cardiovascular Disease: Cardiologist's Perspective

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Conflict of Interest
The author has no financial conflicts of interest.

ABSTRACT

Type 2 diabetes mellitus (T2DM) is a complex disorder and is associated with an increased risk for developing atherosclerotic cardiovascular disease. Control of major risk factors of T2DM can reduce major adverse cardiovascular events (MACEs) in patients. Glycemic control has long been the gold standard for treatment of T2DM. However, strict blood glucose control strategies have repeatedly failed in the prevention of cardiovascular events in key clinical trials. The 2019 American and European practice guidelines for the prevention of cardiovascular disease in patients with T2DM have recommended the use of novel hypoglycemic agents, such as sodium glucose transporter 2 inhibitors and glucagon-like peptide-1 receptor antagonist, which have shown significant reductions in the risk of MACE in spite of their modest glycemic control capacity. A paradigm shift from the glucose-centered approach in treating diabetic patients with cardiovascular disease is imperative. Based on positive outcomes from previous evidence, the reduction of the risk of MACE should be a primary objective for treatment.

Keywords: Cardiovascular diseases; Diabetes mellitus, type 2; Glucagon-like peptide-1 receptor; Sodium-glucose transporter 2 inhibitors

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex and heterogenous disorder which is associated with an atherogenic lipid profile, high blood pressure, low-grade inflammation, renal impairment and advanced glycation end products, all of which increase the cardiovascular risk.[1] Atherosclerotic cardiovascular disease (ASCVD), including coronary heart disease, cerebrovascular disease, and peripheral arterial disease, is the leading cause of morbidity and mortality in individuals with T2DM. The life expectancy of a 50-year-old with T2DM is, on average, 6 years shorter than that of an individual without diabetes mellitus, with approximately 60% of the survival difference attributable to excess cardiovascular deaths.[2]

Improved control of modifiable risk factors has reported a progressive decline in major adverse cardiovascular events (MACEs) during the last 2 decades in both type 1 and T2DM.[3,4] Fatal cardiovascular outcomes were reduced among patients with T2DM although, the excess

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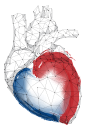

risk in patients with T2DM remains high compared with non-diabetics.[5] The elevated risk of coronary artery disease begins at a lower cut-off point of glucose levels than T2DM (<126 mg/dL) and increases with increasing glucose levels.[6][7] The prevalence of T2DM is high in patients with ischemic heart disease and contribute to poor clinical outcome. A systematic assessment of glycemic and metabolic status is essential in all patients with ASCVDs.

CAN BLOOD GLUCOSE CONTROL PREVENT CARDIOVASCULAR COMPLICATIONS? – A REVIEW OF THE EVIDENCE

The prevention of macrovascular complications of T2DM requires a multifactorial approach addressing all major modifiable risk factors.[8] Therapeutic lifestyle modification is the most important aspect in the management of T2DM. Counseling on a healthy diet, regular physical activity, weight loss, and smoking cessation, control of blood pressure and low-density lipoprotein (LDL) cholesterol provide substantial improvements in cardiovascular complications of T2DM. There is a lack of sufficient evidence of cardiovascular risk factor control in reducing MACE. However, in a study by Ali et al.,[9] smoking among the enrolled patients was high, and almost half of the diabetic patients did not reach the recommended targets for diabetes management. The cardiovascular prognosis of intensive glucose control and the therapeutic effects of different glucose-lowering agents remain controversial in T2DM.[10] Role of intensive glycemic control for protection against microvascular complications and cardiovascular disease (CVD) in patients with type 1 diabetes mellitus is well established.[11][12] However, the effect of blood glucose lowering treatment to prevent MACE and microvascular complications has not been established in patients with T2DM.

Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed that intensive glycemic control reduced the rate of progression of diabetic retinopathy.[13] However, Veterans Affairs Diabetes Trial (VADT), intensive glucose control failed to show significant effects on severe microvascular complications including severe renal changes, decreased glomerular filtration rate, laser treatment, cataract extraction, vitrectomy, and new neuropathy during a follow-up period of 5 to 6 years.[14] Similar results were described in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial.[15] Intensive glucose control only reduced the progression of macroalbuminuria. However, there were no changes in the incidences of severe nephropathy and retinopathy with intensive glucose control.

UK Prospective Diabetes Study (UKPDS) trial was conducted in patients with recently diagnosed or new onset T2DM. In this trial, intensive glucose control was associated with a non-significant reduction of 16% in the relative risk of myocardial infarction (MI).[16] Reduced risk for MI and mortality from any cause with intensive glucose control were observed only with extended post-trial follow-up, a so-called "legacy effect." However, intensive glucose control did not reduce MACE in the long-term or previously diagnosed T2DM in the VADT, ACCORD, or ADVANCE trials. Although, these trials were medium term studies. Furthermore, the ACCORD study reported a 22% increase in total deaths in the intensive-therapy group. In the meta-analysis including the UKPDS, VADT, ACCORD, and ADVANCE trials, intensive glycemic control offers a modest but significant cardiovascular benefit. Although, all-cause and cardiovascular mortality are not benefited.[10] The effect on MACE

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is driven by a 15% reduction in the risk of MI. However, an increased intensive glycemic control was associated with a greater than doubling in the risk of severe hypoglycemia. T2DM patients with no history of macrovascular disease experienced cardiovascular benefits, whereas T2DM with prior macrovascular disease did not. In the VADT sub-study, intensive glycemic control was less effective in reducing the risk of cardiovascular events in T2DM patients with high coronary artery calcium scores at baseline than those with lower coronary artery calcium scores.[17]

In the VADT follow-up study, intensive glucose control did not show the "legacy effect" on the mortality[18] which is consistent with the findings of the ACCORD and ADVANCE follow-up studies. Conversely, results of Diabetes Control and Complications Trial (DCCT) and UKPDS follow-up studies observed mortality benefits regarding CVD and a "legacy effect".[12)16)]

Several explanations have been proposed regarding no "legacy effect" in the VADT, ACCORD, and ADVANCE follow up studies. While DCCT and UKPDS trials were conducted in patients with recently diagnosed or new onset T2DM, the VADT, ACCORD, and ADVANCE trials involved older patients with long-standing T2DM. Advanced atherosclerosis and cardiovascular disease of these T2DM patients did not benefited by intensive glucose lowering. In the DCCT and UKPDS trials, the small proportion of patients took statins and tight blood-pressure control. Whereas, participants in the VADT, ACCORD, and ADVANCE trials have had aggressive treatment for all cardiovascular risk factors including widespread statin use. The cardiovascular protective effects of tight glycemic control may have been less because other cardiovascular risk factors are well controlled by medications.

Statins and novel antihypertensive agents including angiotensin converting enzyme inhibitors/receptor blockers are drugs that can be administered using simple regimens and are relatively free from side effects. However, glucose-lowering therapies are associated with a wide range of unwanted consequences. Concern over the cardiovascular safety of hypoglycemic agents such as sulfonylureas (including rosiglitazone,[19] pioglitazone,[20] and tolbutamide[1)21)22)]) and muraglitazar[23] has been raised and the FDA announced a new guidance that all AHAs for T2DM must thenceforth demonstrate cardiovascular safety in 2008.[24]

UKPDS compared the effects of insulin or sulfonylurea therapy with metformin. Metformin reduced MI by 39%, coronary death by 50%, and stroke by 41% over a median period of 10.7 years in newly diagnosed overweight patients with T2DM without previous CVD.[16] However, metformin has not undergone a randomized, placebo controlled clinical trial to show non-inferiority regarding cardiovascular outcomes in patients with T2DM and CVD.

NOVEL AGENTS SHOWING CARDIOVASCULAR BENEFIT DESPITE WEAK GLUCOSE-LOWERING POTENCY

In recent large-scale cardiovascular outcome trials, sodium glucose transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor antagonists (GLP-1RAs) have been shown to reduce MACEs in patients with T2DM and CVD, or in those with very high/high CVD risk.[25] The SGLT2 inhibitors and GLP-1RAs have been shown to reduce MACE in participants who were treated with metformin at baseline. T2DM and CVD patients treated with metformin should be prescribed an SGLT2 inhibitor or GLP-1RA if HbA1c is above target. In the 2019 American College of Cardiology/American Heart Association guidance on the primary

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prevention of CVD, both classes of drugs are recommended as second-line agents for adults with T2DM and risk factors for ASCVD.[26] The European Society of Cardiology has also recommended these drugs as first-line in high or very high risk groups.[27] Further, the European Society of Cardiology guidelines now advocate SGLT2 inhibitors as first-line agents in high-risk patients.

Major reductions in the MACE with these novel agents, that only achieve modest improvements in glycemic control, highlight the importance of the selection of hypoglycemic agents to reduce the risks of cardiovascular events and mortality among high risk patients with T2DM. In these patients, glycemic control obtained with previous well-established glucose-lowering medications, that is, different combinations of metformin, sulfonylureas, thiazolidinediones, glinides, and insulin, is unlikely to reduce MACE. Thus, glucose control in long-standing T2DM may need to be changed to the evidence-based approach instead of the glucose-centered approach. HbA1c-guided intensive glycemic control may have beneficial effects, especially if severe hypoglycemia is avoided, earlier in the disease course. Hypoglycemic agents with proven cardiovascular efficacy should be incorporated into the treatment regimen, irrespective of HbA1c targets. In this paradigm, first-line therapy would include medications shown to reduce cardiovascular complications and mortality, adding additional medications stepwise from other classes.[28] These medications would be titrated to target doses studied in randomized trials, irrespective of HbA1c levels. Once the doses administered in the cardiovascular outcome trials that demonstrated cardiovascular benefits are reached, HbA1c levels can be checked to assess if it is at a patient-specific target. If HbA1c levels are beyond the individualized targets, additional medications with proven cardiovascular safety can be considered, including dipeptidyl peptidase-4 inhibitors. If, at any point, improved glycemic control is deemed necessary, long-acting basal insulin with either degludec or glargine could be considered. In addition to lowering HbA1c levels, GLP-1RAs have consistently been shown to lower blood pressure and induce weight loss (although this varies across the GLP-1RA class), with greater effects seen in those with higher baseline weight.[29]

As the glucose-lowering effects of SGLT2 inhibitors diminish in patients with renal dysfunction, SGLT2 inhibitors may not be suitable for patients with renal impairment.[30] However, recent trials have shown improved renal outcomes with SGLT2 inhibitors in patients with and without established renal disease.[31] Heart failure is a common complication among patients with T2DM and is associated with a significantly increased risk of subsequent morbidity and mortality. Therapeutic strategies were still lacking to attenuate excess risk of heart failure in this population.[32] In 3 large cardiovascular outcomes trials, SGLT2 inhibitors have shown consistent reductions in heart failure events among patients with T2DM with CVD.[33-35] The reduction in the risk of hospitalizations due to heart failure occurred within initial few weeks of therapy. This class effect is consistent across all three SGLT2 inhibitors.[36]

CONCLUSION

Therapeutic strategies primarily focusing on glycemic control do not adequately optimize the cardiovascular risk in patients with T2DM. Comprehensive and complex approaches for hypertension, dyslipidemia, and other cardiovascular risk factors are essential to prevent cardiovascular morbidity and mortality in T2DM. Tight glucose control is challenging to achieve, and has a greater negative impact on quality of life than lowering cholesterol or

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blood pressure. Novel hypoglycemic agents, such as SGLT2 inhibitors and GLP-1RAs, have shown significant reductions in the risk of MACE with modest glycemic control. These novel hypoglycemic agents show great promise in transforming the treatment of T2DM and concomitant CVDs by independently improving cardiovascular outcomes.

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