The Current Role of Glucose Control Medications in Primary and Secondary Prevention for Cardiovascular Disease

Abstract

Except for glucose management, prevention of CVD follows the same general principles as those for people without DM. The goal of this manuscript is to review the pharmacological strategies aimed at controlling blood glucose that were proven to be useful to prevent death related to CVD.

The importance of intensive glucose lowering with respect to micro vascular risk complications in newly diagnosed patients with DM has been well established. The UKPDS 34 Trial supported the systematic and current use of metformin as a first-line drug therapy for patients with DM and established the great importance of intensive glucose lowering with this drug in order to promote CVD risk reduction in patients with DM.

The recent use of glucagon-like peptide 1 analogues to treat diabetic patients had controversial results with a worse evolution of heart failure patients but had a better renal prognosis in non heart failure patients.

New anti diabetic drugs can also be used to reduce the incidence of future cardiovascular events. Two SGLT2 inhibitors (Empagliflozin and Canagliflozin) have lessened CV Mortality and HF in high risks patients with prior CVD or with a high cardiovascular risk.

Early evidence suggests no CVD benefit with short-term use of dipeptidyl peptidase 4 (DPP-4) inhibitors in people at high risk for CVD. Pioglitazone can also be useful to reduce the incidence of myocardial infarctions and stroke, but did not have an impact on total mortality in patients without established DM.

There is no doubt about the importance of intensive glucose lowering (only reached with the use of Insulin) in patients with type 1 DM. Further studies are needed on metformin and GLP-1 receptor agonists in patients with type 1 DM to determine whether they improve glycemic control, aid in weight reduction and improve clinical outcomes.

Keywords: Cardiovascular mortality; Cardiovascular prevention; Diabetes mellitus; Cardiovascular risk

Introduction

In most developed countries cardiovascular diseases (CVD) remain the main cause of morbidity and mortality in the general population, especially among the elderly [1]. CVD causes 18 million deaths per year globally and a similar number of nonfatal cardiovascular events [2]. People with Diabetes mellitus (DM) are on average at double the risk of CVD [3]. Cardiovascular disease (CVD) prevention, i.e. coronary heart disease, stroke, and peripheral artery disease, includes all the actions intended to eliminate or reduce the impact of these disorders and their disabilities in the population or even targeted at individuals.

Except for glucose management, prevention of CVD follows the same general principles as those for people without DM. Achieving low BP levels and low LDL-C and total cholesterol concentrations are particularly important. Many treatment targets are more stringent for patients with DM [4]. Typically patients with type 2 DM (T2DM) have multiple CVD risk factors, each requiring treatment according to existing guidelines. The goal of this article is to review the pharmacological strategies aimed to control blood glucose that were proven to be useful in preventing death related to CVD.

Discussion

Biguanides have many theoretical benefits over other agents in the treatment of T2DM including reducing hepatic gluconeogenesis, decreasing plasma insulin levels, and facilitating weight loss. However, the biguanide phenformin was associated with increased CV and all-cause mortality in UGDP [5].

In the UK, Prospective Diabetes Study 33 (UKPDS 33) established the importance of intensive glucose lowering with respect to micro vascular risk complications in patients newly diagnosed with DM. In this important and historical trial, intensive blood glucose control by either sulphonylureas or insulin substantially decreased the risk of micro vascular
complications, but not macro vascular disease, in type 2 diabetic patients. None of the individual drugs had an adverse effect on cardiovascular outcomes. All intensive treatment increased the risk of hypoglycemia [6].

Published simultaneously with the above, the UKPDS 34 Trial supported the systematic and current use of metformin as a first-line drug therapy for patients with DM and established the great importance of intensive glucose lowering with this drug in order to promote CVD risk reduction in patients with DM. In this important and historical trial 1,704 overweight patients with newly diagnosed T2DM were randomized to one of three arms: conventional therapy with diet alone, intensive therapy with metformin, or intensive therapy with an early-generation of antiglycemic agents (chlorpropamide, glibenclamide, or insulin). The primary analysis compared metformin to diet alone, with a secondary analysis comparing metformin to intensive therapy with the other agents. With a median follow-up of 10.7 years, metformin was associated with a reduction in DM-related complications and in all-cause mortality when compared to the other two arms of therapy [7]. These benefits persisted for an additional 10 years of follow-up [8]. These studies form the basis for the early administration of metformin in overweight patients with T2DM.

The benefits of metformin monotherapy in overweight patients with T2DM was further solidified by a 2005 Cochrane review of 29 randomized trials comparing metformin to conventional therapy with diet or other modern antiglycemic agents. This meta-analysis demonstrated a benefit for metformin monotherapy across a diverse range of outcomes including glycemic control, weight loss, lipid and blood pressure control, diabetes-related mortality, all-cause mortality, and incidence of myocardial infarction [9].

Since the publication of UKPDS 34, several generations of antiglycemic agents have been developed, and direct comparisons with metformin have been performed both prospectively and retrospectively. The large multicenter Spread-Dimcad trial (2013) trial (2013) randomized patients with T2DM and CAD to either metformin or glipizide for 3 years. At a median follow-up of 5 years, both groups achieved goal HbA1c levels (7.1% vs. 7.0%) but metformin was associated with a 12% absolute risk reduction in the composite primary outcome of nonfatal MI, nonfatal stroke, revascularization, CV mortality, or all-cause mortality [10].

Recent trials using newer therapies like dipeptidyl peptidase-4 demonstrated non inferiority (safety) in cardiovascular outcomes among patients with T2DM and existing CVD or at higher risk of events [11-14]. Recently, for example, the use of sitagliptin in more than 7,000 patients - in the TECOS trial - was not associated with an increased risk of heart failure or related adverse outcomes after Sitagliptin therapy.11 There was, however, an increase in the rate of hospitalization for HF with the use of saxagliptin (SAVOR-TIMI 53) trial [14].

The glucagon-like peptide 1 analogue is another type of anti-diabetic drugs that had controversial results in outcomes among diabetic patients in recent trials. The use of Liraglutide in patients with high-risk heart failure patients with reduced ejection fraction (FIGHT) was associated with an almost 30% increase in the rates of death or heart failure hospitalization within 6 months [15].

Very recently, the use of the same GLP1 analogue in type 2 diabetic patients without heart failure was associated with lower rates of the development and progression of diabetic kidney disease than placebo [16]. These results suggests that the use of this type of anti-diabetic drugs could be associated with less future kidney aggressions (manifested by a lower rate of micro albuminuria), but with higher rates of hospitalization or death in patients with severe heart failure.

More recently, a newer type of anti diabetic drug has shown incredibly good results for secondary prevention of new cardiovascular events in diabetic patients: the Sodium-glucose co-transporter-2 inhibitors (SGLT2i). Empagliflozin, one of these SGLT2i, was the first to demonstrate unequivocal benefit in the cardiovascular outcome of diabetic patients with a history of a prior cardiovascular event (heart attack, stroke or others). In the EMPAREG OUTCOME trial, 7020 patients were randomized to use Empagliflozin added to standard anti-diabetic treatment or standard treatment alone. Patients using this SGLT2i presented a 38% reduction in CVD death, all-cause mortality (32%) and also in the hospitalization for heart failure (35%). In this study, the results of non-fatal myocardial infarction and stroke were not reduced. This fact, added to the rapid separation of mortality curves, suggests that the mechanism of benefit was likely to relate more to cardio-renal haemodynamic effects than to atherothrombotic actions or effects of glucose lowering per se [17].

The use of Canagliflozin (another type of SGLT2i) was also related to the reduction of cardiovascular and renal events in type 2 diabetic patients. This time, this type of drug was used for primary (not secondary) prevention of cardiovascular events. The CANVAS Program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. Participants in each trial were randomly assigned to receive Canagliflozin or placebo and were followed for a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Patients treated with Canagliflozin, had a significantly lower risk (14%) of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke than those who received placebo, although this treatment led to a greater risk of peripheral amputation (primarily at the level of the toe or metatarsal; 1.97 times more events) and infection of male genitalia (3.2 times more events) [18]. Another recently published meta-analyses (The CVD-Real study) also showed lower rates of hospitalization for heart failure (39%) and all cause mortality (51%) in new users of three different SGLT2i (predominantly Canagliflozin and Dapagliflozin and a lower proportion of Empagliflozin) when compared with standard glucose treatment with the use of other types of medication for diabetes mellitus [19].

Another anti diabetic drug that also demonstrated some impact in the reduction of new cardiovascular events that we must highlight in this summary was Pioglitazone. In the IRISTrial (a multicenter, double-blind trial), 3876 patients who had had a recent ischemic stroke or transient ischemic attack (TIA) were randomly assigned to receive either pioglitazone (target dose of 45 mg daily) or placebo. At the time of randomization, eligible patients did not yet have the diagnosis of diabetes but were found to have insulin resistance (a high HOMA-IR index). The primary
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Conflicts of Interest

Authors declare there is no conflict of interest in composing this manuscript.

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