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A review of the efficacy and safety of several antihyperglycemic medications in the management of cardiovascular disease in diabetes

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Abstract

Diabetes is a worldwide public health problem affecting millions of people. By 2030, the incidence of diabetes is expected to increase to 4.4% of the global population, an equivalent of approximately 366 million people. This growth of the "diabetes pandemic" is even more pronounced in certain countries including the United States, which is expected to have a 165% increase in prevalence by 2050 compared to that in 2000. Diabetes is a leading cause of morbidity and mortality, which results from microvascular or macrovascular disease. Compared to non-diabetic individuals, diabetics have higher risk of coronary artery disease, cardiac ischemia, cerebrovascular disease, and peripheral vascular disease. Myocardial infarction is nearly 1.8 times more frequent in diabetic patients compared to non-diabetic equivalents. Patients with diabetes also have a high burden of atherosclerotic disease risk factors like hypertension, hyperlipidemia, and obesity. Managing hyperglycemia has been and remains at the center of managing diabetes and preventing its complications. Since 1923 when insulin was first introduced, several hypoglycemic agents have emerged. Experimental and clinical studies have examined the efficacy of these medications in preventing cardiovascular complications and whether a certain drug class has an inherent protective role independent of its hypoglycemic effect. This review will shed light on the evidence regarding the cardiovascular protective role of current hypoglycemic agents.

Introduction

The American Diabetes Association reports that in 2012 21 million Americans were suffering from diabetes, 8.1 million diabetics remained undiagnosed and another 86 million individuals had prediabetes [1]. Diabetes is the seventh leading cause of death in the United States but may be significantly under-reported. After adjusting for age differences the cardiovascular disease death rate is 1.7 times higher among adults with a diagnosis of diabetes than it is among their non-diabetic counterparts. Myocardial infarction is 1.8 times more frequent and stroke is 1.5 times more frequent in adults with diabetes. Approximately 60% of non-traumatic lower extremity amputations occur in individuals with diabetes as well. The vascular complications of diabetes are described as microvascular diseases including retinopathy, neuropathy, and nephropathy and macrovascular diseases such as cardiovascular and peripheral vascular disease. And while the microvascular complications certainly contribute to disease morbidity it is the macrovascular disease which affects mortality. After many years without new treatment options, a number of new classes of drug therapies for diabetes have been developed. Some claim to impact cardiovascular outcome. For the most part, with the exception of metformin, the different classes of oral anti-diabetic agents are treated with equality by the clinical practice guidelines with respect to achieving A1c goal [2]. However, it may be time to consider cardiovascular outcome data when choosing a particular agent. This review summarizes the various classes of oral anti-diabetic agents with respect to cardiovascular and peripheral vascular disease data.

Sulfonylureas

Sulfonylureas have been available for more than 50 years. They stimulate insulin secretion by the pancreatic beta cell. They are relatively safe, inexpensive and well tolerated for the most part. One of the earliest studies questioning the cardiovascular risks associated with sulfonylureas was the University Group Diabetes Program (UGDP) trial [3] in which investigators recommended early termination of the tolbutamide arm of the study because of excess cardiac deaths (12.7%) compared to placebo (4.9%). There were many criticisms of the UGDP study including poor randomization, poor verification of cause of death, poor methodology etc., all of which led to the second larger UK Prospective Diabetes Study (UKPDS) [4] nearly thirty years later. Although the primary aim of the study was to determine the effect of intensive glycemic control, a number of additional studies were embedded into the protocol to compare the effects of different diabetes treatments on any diabetes endpoint. The effects of tighter glycemic control reduced microvascular complication rates, but effects on macrovascular disease were not statistically significant. However, there was no evidence that the sulfonylureas, glyburide and chlorpropamide, were associated with increased mortality. The controversy enjoyed a

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brief respite. Later the discovery that sulfonylurea receptors (SUR1) on the pancreatic beta cells were different from sulfonylurea receptors on cardiacmyocytes (SUR2A) and smooth muscle cells (SUR2B) suggested that the effects of the second generation sulfonylureas such as glimepiride were more tissue specific and did not inhibit the myocardial ischemic protective effect of the K^+-ATP channels in the heart and smooth muscle vasculature and offered some insight into why cardiovascular outcome data from the sulfonylureas might be contradictory [5]. This finding plus later data on other hypoglycemic agents led to a number of meta-analyses and observational studies summarized nicely in a review by Abdelmoneim, *et al.* [6]. In summary, the strength of the data on increased cardiovascular risk associated with sulfonylurea use remains weak.

Benzoic acid derivatives

The meglitinide drug class of oral hypoglycemics are the benzoic acid derivatives repaglinide and nateglinide. They may be thought of as the short-acting cousins of the sulfonylureas or nonsulfonylurea secretogogues. Repaglinide targets SUR1 ansd SUR 2 receptors [7] whereas nateglinide [8] has a higher selectivity for the SUR 1 receptor. There are no long-term trials evaluating cardiovascular events or mortality in patients using these agents.

Metformin

Metformin is a biguanide. Its mechanism of action is to reduce hepatic glucose output and increase glucose uptake in other tissues especially muscle thereby increasing insulin sensitivity. Metformin has also been shown to have a direct action in protecting against hyperglycemia-induced endothelial dysfunction through reduction of oxidative stress, protecting endothelial nitric oxide synthase, and reduction of mitochondrial stress [9]. The metformin alone arm of the UKPDS study revealed a 39% reduction in myocardial infarction [10]. However, when metformin was added to a sulfonlyurea to achieve glycemic control cardiovascular mortality but not risk of myocardial infarction increased. Subsequent studies have not supported this finding. In a study of more than 8000 new users of metformin and sulfonylurea [11] followed over five years, mortality rates for metformin users were 13.8% compared to 13.6% for combination users and 24.7% for sulfonylurea users. Furthermore, mortality benefit from metformin did not appear to be affected by which agent was used first.

Metformin can also add risk reduction to other classes of hypoglycemics.In two large retrospective database analyses, [12,13] metformin was also shown to reduce the incidence of congestive heart failure. Combination of metformin with a thiazolidinedione improved the reduction in risk of both heart failure and cardiovascular events [13]. In a substudy of the SCOUT trial, diet alone, metformin alone, metformin plus sulfonylurea or metformin plus insulin in diabetics at high risk of cardiovascular disease found that only diet alone or metformin alone lowered the incidence of primary cardiovascular outcomes. When combined with a DPP-4 inhibitor, the metformin-DPP4 inhibitor treatment arm had 5.3 events per 1000 person years compared to 11.3 events for the metformin-sulfonylurea arm as well as a reduction in all-cause mortality [14]. Thus there is little doubt of metformin's value as a first line agent for treatment of type 2 diabetes in the absence of contraindications because of its potential for cardiovascular risk reduction.

Thiazolidinediones; Cardiovascular disease

The thiazolidinediones activate a group of nuclear receptors known as PPARs (peroxisome proliferator-activated receptors) responsible for decreasing insulin resistance, differentiating adipocytes, inhibiting VEGF-induced angiogenesis, decreasing leptin, lowering certain interleukins and exerting an anti-proliferative action. They are postulated to exert a cardiovascular benefit through their effects on endothelial function, inflammation and lipid particle makeup. Troglitazone was removed from the market due to an increased incidence of drug-induced hepatitis leaving rosiglitazone and pioglitazone. In experimental models of ischemia and reperfusion, the thiazolidinediones [15,16] reduced infarct size and improved ventricular remodeling. Then in clinical trials the drugs were shown to prevent myocardial infarction [17], reduce neointimal proliferation and restenosis after coronary stenting [18] and induce regression of atherosclerosis based on intravascular ultrasound [19].

Unfortunately, a meta-analysis of 42 trials, including DREAM [20] and ADOPT [21], on the effects of rosiglitazone on cardiovascular outcomes [22] reported an odds ratio of 1.43 for myocardial infarction and 1.64 for all-cause mortality in the rosiglitazone group. Later trials of rosiglitazone comparing intensive therapy to standard therapy including the Veterans' Affairs Diabetes Trial (VADT) [23] and the ACCORD trial [24] showed no association of rosiglitazone with increased myocardial infarction risk. The FDA restricted use of the drug in 2010. An early interim analysis of the RECORD trial showed no increase in cardiovascular outcomes in patients treated with rosiglitazone combined with metformin or sulfonylurea compared to metformin or sulfonylurea alone [25] but the results were considered inconclusive due to the low overall cardiovascular event rate. The FDA later lifted the restrictions in 2013 [26].

The BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial compared [27] revascularization plus intensive medical therapy versus medical therapy alone and insulin-sensitization therapy to insulin-providing therapy. Sensitization therapy was accomplished with metformin plus thiazolidinedione compared to insulin providing therapy with insulin and sulfonylurea. Although both pioglitazone and rosiglitazone were included, the predominant thiazolidinedione was rosiglitazone. Overall, the revascularization and medical therapy treatment arms had the same rate of cardiovascular events but of those assigned to the bypass grafting arm insulin sensitization provided fewer cardiovascular events, higher HDL levels, less weight gain, and less hypoglycemia suggesting insulin sensitization may be preferable in patients with type 2 diabetes and coronary artery disease.

In the PROactive trial [28], pioglitazone reduced the risk of recurrent nonfatal infarction by 28% and cerebrovascular events by 47% in patients with established cardiovascular disease although the composite primary endpoint was reduced by only 10%.A randomized clinical trial comparing the safety and efficacy of rosiglitazone versus pioglitazone was completed in October 2016, but results are not yet available [29].

Thiazolidinediones: Congestive heart failure

Diabetes is an independent risk factor for congestive heart failure and left ventricular dysfunction. Thiazolidinediones, by virtue of their effects on the renal tubule, may result in fluid retention and edema and are best avoided in patients with heart failure [30]. Newer agents such as the DPP-4 inhibitors, the GLP-1 agonists and the SGLT 2 inhibitors discussed below are other options for heart failure patients. However, the thiazolidinediones appear to be safe for heart failure patients in combination with metformin [27].

DPP-4 inhibitors

The dipeptidyl peptidase-4 (DPP-4) inhibitors are a newer class of

oral glucose lowering agent that improves glucose control by inhibiting the enzymatic degradation of incretins such as glucagon like peptide and gastric inhibitory peptide which are secreted in response to a meal [31]. These incretins then inhibit the release to glucagon resulting in increased insulin secretion and delays gastric emptying. Therefore, their effect is predominantly through reduction in postprandial glucose levels. Preclinical data, however, suggested they might also have beneficial cardiac effects through actions on other vasoactive peptides. The drug class is weight neutral, lowers postprandial lipemia, improves platelet aggregation and reduces oxidative stress [32]. Three large comparative trials, TECOS, EXAMINE and SAVOR-TIMI 53 studied the cardiovascular safety of the DPP-4 inhibitors.

The TECOS [33] trial was an FDA- mandated study to assess the cardiovascular safety of sitagliptin in the post-rosiglitazone period. TECOS was a well-designed randomized, double-blinded, placebo-controlled trial comparing sitagliptin to placebo as add-on therapy for uncontrolled type 2 diabetes in patients with known cardiovascular disease. The primary outcome was non-inferiority for cardiovascular death, nonfatal MI, nonfatal stroke or hospitalization for unstable angina. The secondary composite endpoint was superiority for cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Sitagliptin was effective at lowering A1c but was found to be non-inferior although not superior to placebo for the primary cardiovascular endpoint. Alogliptin [34] was also shown to have a cardiovascular risk factor similar to placebo with the exception of a 3.9% versus 3.3% increase in the incidence of congestive heart failure.Those taking alogliptin were also significantly more likely to have their first hospital admission for heart failure (2.2 *vs*1.3%). The SAVOR-TIMI [35] trial evaluated saxagliptin versus placebo. Saxagliptin was found to have similar rates of MI, stroke, cardiovascular revascularization and unstable angina compared to placebo, however, the incidence of congestive heart failure was 3.5% for saxagliptin versus 2.8% for the placebo group. As a result, the FDA issued an advisory warning regarding heart failure risk to the alogliptin and saxagliptin drug labels [36]. Later, a much larger cohort study of more than 78,000 saxagliptin and 298,000 sitagliptin users did not find an increased risk of hospitalization for heart failure among either "gliptin" user compared to other glucose-lowering "non-gliptin" agents [37]. The FDA issued an update to their original warning regarding heart failure risk and use of saxagliptin or alogliptin, but did not remove the warning [38].

Currently, the DPP-4 inhibitors are recommended as second line agents by the clinical practice guidelines [2]. For the most part they are well tolerated and can be taken without regard for food. They have few drug interactions although saxagliptin has an active CYP3A4/5 metabolite which requires dosage adjustment with concurrent use of CYP3A4/5 inhibitors. The serious side effect of pancreatitis has been anecdotally reported with all DPP -4 inhibitors [39]. Therefore, DPP-4 inhibitors should be used cautiously in patients with a history of pancreatitis [40].

GLP-1 agonists

The glucagon-like peptide-1 (GLP-1) agonists are inhibitors of GLP-1 released from the digestive tract in response to a meal. These incretin-like peptides lower glucose levels by inhibiting hepatic glucagon release, delaying gastric emptying, enhancing insulin release from the pancreas and possibly increasing beta cell mass [41]. In addition, the discovery of GLP-1 receptors in other organ systems such as the gastrointestinal tract, kidney, myocardium, vascular endothelium, and kidney leads many to hope that the drug class will have a neutral or positive effect on diabetic cardiovascular disease which has thus far been resistant to other forms of glucose-lowering therapy [42]. Wang was able to show a small reduction in systolic and diastolic blood pressure with exenatide and liraglutide [43]. Other studies have reported "modest" improvements in lipid profiles [44], reductions in various cardiovascular markers such as CRP and BNP [45] and improved left ventricular function [46].

Although some cardiovascular outcome data has been acquired from studies such as LEAD [47], HARMONY [48], and AWARD [49], the incidence of cardiac events was not the primary outcome. The ELIXA [50] trial, on the other hand, was a randomized, placebo-controlled trial designed to measure the primary outcome of cardiovascular events in lixisenatide versus placebo. The primary endpoints of cardiovascular death, myocardial infarction, stroke or hospitalization for unstable angina occurred in 13.4% of the lixisenatide group compared to 13.2% of the placebo group. Neither was there an increase in hypoglycemia, pancreatitis, nor pancreatic neoplasms. Lixisenatide was concluded to be a safe hypoglycemic agent without evidence of increased major cardiovascular events or serious side adverse effects. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial also specifically addressed cardiovascular outcomes [51]. It showed that liraglutide was associated with significantly lower rates of death from cardiovascular causes (4.7% in liraglutide group vs. 6.0% in placebo group), and death from any cause (8.2% in liraglutide group compared to 9.6% in placebo group). However, the rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were not significantly different between the two groups.

In summary, a number of meta-analyses have looked at cardiovascular event rates in the DPP-4 inhibitors and the GLP-1 receptor agonists. However, data is inconclusive due to the small number of available trials for individual agents, different study populations and variations in study design, etc. It remains unclear which groups of patients are likely to experience benefit or harm. The GLP-1 agonist class of antidiabetics appears to be safe for patients with cardiovascular disease but is probably not the best option for patients with a history of pancreatitis, alcoholism, pancreatic neoplasm, severe hypertriglyceridemia or severe renal disease [52]. Long term safety and benefit have not been definitively established and the results of ongoing cardiovascular outcome trials should be awaited [53].

Sodium-glucose cotransport 2 inhibitors

The GLUT-1 and 2 cotransporters are Na/ATPase-driven glucose channels responsible for reabsorption of glucose in various tissues. SGLT-2 is localized to the proximal renal tubule and accounts for up to 90% of renal glucose reabsorption. Blockade of the glucose channel by the SGLT-2 inhibitors or "flozins" leads to significant glycosuria and resultant improved glucose control. This mechanism of action does not correct the underlying altered physiology of type 2 diabetes but does offer some theoretical advantages [54]. The resultant glycosuria produces an osmotic diuresis. This effect on sodium and volume load lowers blood pressure [55] and was postulated to have ancillary beneficial cardiovascular effects [56] in addition their glucose-lowering abilities.

The EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial was a randomized, double-blinded, parallel group trial that studied all-cause mortality, cardiovascular death and hospital admissions for congestive heart failure in diabetics with high cardiovascular risk who were already receiving statins, anithypertensives and anti-platelet therapy

[57]. Of more than 7000 patients treated, the empagliflozin group had a 3.7% versus 5.9% cardiovascular death rate, a 2.7% versus 4.1% heart failure hospitalization rate, and a 5.7% versus 8.3% all-cause mortality rate when compared to placebo. There was no significant difference in incidence of myocardial infarction or stroke. The EMPA-REG trial is currently the only completed trial of SGLT-2 inhibitor effects on cardiovascular disease outcome in type 2 diabetes however other studies remain underway. Whether this cardiovascular benefit is related to empagliflozin's pleomorphic effects or blood pressure and volume changes and whether this is a drug class effect still remain unanswered.

Conclusion

Cardiovascular disease remains the primary cause of death in type 2 diabetes. And though tighter glucose control has clearly reduced microvascular complications, the cardiovascular complications of type 2 diabetes remain frustratingly resistant to medical intervention.

When initiating monotherapy for type 2 diabetes many issues including side effect profile, cost, insurance plan, comorbidities and practitioner comfort are considered. In the absence of contraindications or intolerance, metformin remains the agent of choice for type 2 diabetes. Pioglitazone should probably not be used alone in patients with a history of heart failure but seems to be safe in combination with metformin and also has beneficial effects on lipid profiles.

The DPP-4 inhibitors appear to have neutral to beneficial effects on cardiovascular risk but show mixed results in the case of congestive heart failure with saxagliptin and alogliptin. Both still carry the FDA warnings regarding use when there is potential risk of heart failure.

The GLP-1 agonists appear to be safe in patients at high risk for cardiovascular disease but should be used cautiously if at all in patients with a history of pancreatic disease. Lixisenatide in particular has demonstrated a positive cardiovascular outcome profile. Whether this applies to the entire drug class has not yet been proven. Of the SGLT-2 inhibitors, empagliflozin in particular has positive cardiovascular outcome data. Whether this applies to the entire drug class has not yet been proven.

As always, the most physiologic, least expensive, safest treatment of type 2 diabetes is diet and exercise. When lifestyle changes are no longer sufficient, practitioners now have a large armamentarium of agents from which to choose. Prescribing a particular agent for each individual should take into account the appropriate A1c goal and existing comorbidities especially cardiovascular risk. Cardiovascular disease remains a major health problem.

Disclosures

The authors have no potential conflict of interest to disclose.

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