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Diabetes Drugs and Cardiovascular Safety

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Diabetes is a well-known risk factor of cardiovascular morbidity and mortality, and the beneficial effect of improved glycemic control on cardiovascular complications has been well established. However, the rosiglitazone experience aroused awareness of potential cardiovascular risk associated with diabetes drugs and prompted the U.S. Food and Drug Administration to issue new guidelines about cardiovascular risk. Through postmarketing cardiovascular safety trials, some drugs demonstrated cardiovascular benefits, while some antidiabetic drugs raised concern about a possible increased cardiovascular risk associated with drug use. With the development of new classes of drugs, treatment options became wider and the complexity of glycemic management in type 2 diabetes has increased. When choosing the appropriate treatment strategy for patients with type 2 diabetes at high cardiovascular risk, not only the glucose-lowering effects, but also overall benefits and risks for cardiovascular disease should be taken into consideration.

Keywords: Diabetes mellitus; Cardiovascular diseases; Heart failure; Hypoglycemic agents

INTRODUCTION

Cardiovascular (CV) disease is a highly prevalent complication and the major cause of premature death in patients with type 2 diabetes [1]. The effect of improved glycemic control on CV complication has been well established through clinical trials and meta-analyses [2-5]. However, several studies have suggested that some antidiabetic drugs increase CV risk, despite being effective at lowering blood glucose in type 2 diabetes [6-9]. For this reason, new diabetes agents are required to demonstrate CV safety, showing robust CV outcome data from randomized, controlled trials in order to grant approvals. On the other hand, these regulatory requirements might also provide the opportunity for some of drugs in CV outcome trials to be tested for CV benefits [1].

We will discuss the evidence of the CV risk associated with thiazolidinedione (TZD) use, which aroused awareness of potential CV risk associated with diabetes agents and prompted the U.S. Food and Drug Administration (FDA) to issue new guidelines about CV risk [10]. This study will also review the published or currently ongoing CV safety trial of the dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonist, and sodium glucose cotransporter 2 (SGLT2) inhibitor.

THIAZOLIDINEDIONES

Rosiglitazone

Adverse data from a meta-analysis published in *New England Journal of Medicine* in 2007 evoked concern about a possible

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increased CV risk associated with rosiglitazone use [7,10]. Using a fixed-effects analytic model with data from 42 randomized clinical trials, this analysis concluded that rosiglitazone was associated with an approximately 43% increased risk of myocardial infarction (odds ratio [OR], 1.43; 95% confidence interval [CI], 1.03 to 1.98) and an approximately 64% increased risk of CV death (OR, 1.64; 95% CI, 0.98 to 2.74) [7].

The interpretation of these study results have been debated extensively [11,12]. These meta-analyses consisted of predominantly small, short-term, nonadjudicated treatment trials in lower-risk populations [7,13]. Nissen's analysis used the number of events rather than time to event without consideration of follow-up, and some trials with no events were excluded. None of the trial included in the reports focused primarily on CV safety in patients treated with rosiglitazone [11-13]. Furthermore, studies were combined on the basis of a lack of statistical heterogeneity, despite substantial variability in control groups, inclusion criteria, follow-up, and outcome assessment. Indeed, other researchers have analyzed the same group of studies using different statistical methods and found no link between heart attack and rosiglitazone [11].

Nevertheless, additional meta-analyses suggested an increased risk of adverse CV events among patients with type 2 diabetes treated with rosiglitazone [6,14,15]. Due to this possible association with myocardial infarction, rosiglitazone was withdrawn from the European market by the European Medicines Agency in 2010 [16]. At the same time, the FDA imposed restrictions on the prescription and use of the diabetes drug rosiglitazone [17]; the drug has also been removed from the Korean market.

In 2013, the FDA lifted restrictions on the prescription and use of rosiglitazone after re-evaluation of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, which showed no increase in the risk of CV morbidity or mortality attributable to rosiglitazone [18,19]. The RECORD trial is the only completed prospective trial to evaluate CV safety in patients treated with rosiglitazone [13].

The rosiglitazone experience aroused awareness of potential CV risk associated with diabetes agents and prompted the FDA to issue new guidelines about CV risk. The approval process for new agents must include a demonstration of no unacceptable increase in CV risk [10]. This requires a meta-analysis of important CV events in phase 2/3 to achieve an upper 95% CI <1.3 to qualify for approval without requiring a postmarketing CV trial, provided that the overall benefits and risks support drug approval. If the upper 95% CI is >1.8, additional phase 3 safety studies are required before resubmission for marketing authorization. If the overall risk-benefit balance supports drug approval but the upper CI lies between 1.3 and 1.8, then a postmarketing CV trial usually required to demonstrate an upper 95% CI <1.3 [10,20]. In practice, each sponsor of a recently approved drug has undertaken such a study, even if the phase 2/3 CV events conform to an upper 95% CI <1.3; such postmarketing studies appear to be almost obligatory [10,21].

Pioglitazone

Along with rosiglitazone, pioglitazone is also a member of the TZD class of drugs. Thus, there is a question of whether use of the other marketed TZD, pioglitazone, carries similar risks [15]. A large CV outcomes trial with pioglitazone, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial, was performed to evaluate the effects of pioglitazone on CV morbidity and mortality in high-risk patients with type 2 diabetes. The PROactive trial was a prospective, randomized, controlled trial in 5,238 patients with type 2 diabetes who had evidence of CV disease. These patients were randomized to pioglitazone, titrated to 45 mg daily, or matching placebo with a background of usual glucose-lowering medications. In that study, treatment with pioglitazone produced a nonsignificant reduced risk of coronary and peripheral vascular events (hazard ratio [HR], 0.90; 95% CI, 0.80 to 1.02; P=0.10). As a secondary endpoint, pioglitazone reduced the composite of all-cause mortality, nonfatal myocardial infarction, and stroke (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.03) [22]. More recently, in the Insulin Resistance Intervention after Stroke (IRIS) trial, which included 3,876 nondiabetic patients with insulin resistance and ischemic stroke or transient ischemic attack, patients who were assigned to the pioglitazone group showed a statistically significant 24% reduction in strokes and myocardial infarction compared with placebo recipients over 4.8 years [23]. In addition, a meta-analysis of CV outcome from 19 randomized clinical trials, with a total enrollment of 16,390 diabetic patients, showed that pioglitazone was associated with a significantly lower risk of the composite of death, myocardial infarction, and stroke (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005) [24].

However, there remains a major concern about the increase in heart failure associated with pioglitazone treatment. Serious congestive heart failure was increased by pioglitazone in both the PROactive trial and the meta-analysis, although without an associated increase in mortality [22,24].

DIPEPTIDYL PEPTIDASE-4 INHIBITORS

The DPP-4 inhibitor class of antidiabetic drugs emerged after the FDA issued new guidance about CV risk that requires new diabetes drugs to conduct postmarketing CV trials to show drug safety. In accordance with this new FDA guideline, examination of cardiovascular outcomes with alogliptin versus standard of care in patients with type 2 diabetes and acute coronary syndrome (EXAMINE), Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53), and Trial Evaluating Cardiovascular Outcome with Sitagliptin (TECOS) were conducted to demonstrate CV safety or CV benefit. In the EXAMINE trial, which included a total of 5,380 patients with type 2 diabetes who had experienced either acute myocardial infarction or unstable angina within the previous 15 to 90 days, the rates of major adverse CV events were not increased with the DPP-4 inhibitor alogliptin compared with placebo [25]. In the SAVOR-TIMI trial, 16,492 patients with type 2 diabetes at high risk for CV events or who had a history of CV events were randomized to saxagliptin or placebo. Consistent with the results from EXAMINE, saxagliptin did not increase the risk of CV events [26]. The TECOS trial also produced consistent findings of no CV risk associated with sitagliptin [27]. However, none of these trials demonstrated a CV benefit of DPP-4 inhibitors [25-27].

It is important to note that these trials have raised concerns about the increased rate of heart failure associated with DPP-4 inhibitor use, with ongoing uncertainty regarding the validity of the findings and their clinical implications [28,29]. Saxagliptin use was associated with a 27% increase in hospitalization for heart failure in the SAVOR-TIMI trial [26]. This increase in risk was highest among patients with elevated levels of natriuretic peptides, prior heart failure, or chronic kidney disease [30]. Alogliptin use was also associated with a numerically higher but not statistically significant increased risk of hospitalization for heart failure in the EXAMINE trial [25]. In a 12-month VIVIDD (Vildagliptin in Ventricular Dysfunction Diabetes) trial, which randomized 254 patients with type 2 diabetes and New York Heart Association functional class I to III heart failure to vildagliptin or placebo, there was no difference in left ventricular function and no excess of heart failure hospitalization with vildagliptin. However, despite a significant decrease in plasma level of brain natriuretic peptide, patients treated with vildagliptin had an increase in left ventricular end-diastolic volume, and there were numerically more deaths in the vildagliptin arm compared with the placebo arm, raising additional concerns about safety with DPP-4 inhibitors in patients with established heart failure [31-34]. Meta-analyses of these and other DPP-4 inhibitor studies suggest that these agents are associated with increased risk of hospitalization for heart failure [34-36].

There are no specific mechanistic reasons to attribute an increase in heart failure outcomes to the pharmacological properties of the DPP-4 inhibitor [34]. In addition, the most recent large-scale TECOS findings did not confirm the findings of increased risk of hospitalization for heart failure [37]. At this time, it is unclear whether increased risk of heart failure hospitalization is a class effect of DPP-4 inhibitor. In order to elucidate and interpret the concern about hospitalization for heart failure with DPP-4 inhibitors, further large-scale CV outcome studies need to be conducted; such work is ongoing (CAROLINA [Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes], Clinical Trial.gov number, NCT01243424) [10,34].

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

As with DPP-4 inhibitor, CV safety studies for GLP-1 receptor agonists were designed to satisfy the requirement of the 2008 FDA guidance [10]. The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial is the first completed study of GLP-1 receptor agonist and did not show a benefit on CV outcomes in the 6,068 patients with type 2 diabetes at high CV risk. There was no difference between the lixisenatide and placebo group in the primary composite outcome of CV death, myocardial infarction, stroke, or hospitalization for unstable angina [38]. Some trials and meta-analyses have raised concerns about the increased rated of heart failure associated with DPP-4 inhibitor use [25,26,31,34-36]. Along with DPP-4 inhibitor, GLP-1 receptor agonist is also a member of the incretin-based drug family [39]. However, the ELIXA study has shown a neutral effect on the incidence of hospitalization for heart failure among patients randomly assigned to lixisenatide, which was consistent in the subgroups of patients who had experienced heart failure and those who had not [38].

CV safety studies with other GLP-1 receptor agonists (LEADER [Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results], Clinical Trial.gov number, NCT01179048; EXSCEL [Exenatide Study of Cardiovascular Event Lowering Trial], NCT01144338; REWIND

[Researching Cardiovascular Events with a Weekly Incretin in Diabetes] with dulaglutide, NCT01394952; SUSTAIN 6 [Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes 6], NCT01720446) are ongoing; their results are expected to provide new information on CV safety or benefit regarding this GLP-1 receptor agonist [10]

SODIUM GLUCOSE COTRANSPORTER-2 INHIBITORS

EMPA-REG OUTCOME is a CV safety trial of an agent from the SGLT2 inhibitor class. This trial was performed to evaluate the effects of empagliflozin on CV morbidity and mortality in patients with type 2 diabetes at high CV risk. A total of 7,020 patients with diabetes and established CV disease were randomly assigned in a 1:1:1 ratio to receive either 10 or 25 mg of empagliflozin or placebo once daily on a background of standard care (including dyslipidemia-, hypertension-, and glucose-lowering therapy). In this study, the pooled empagliflozin group has shown a statistically significant 14% reduction in the primary composite major adverse cardiac event endpoint (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) compared with placebo recipients over a median of 3.1 years [40].

The difference in this primary end point was mainly driven by the 38% relative risk reduction in CV death. Whereas the reduced CV death was accompanied by 35% decreased hospitalization for heart failure, treatment with empagliflozin did not reduce the risk of nonfatal myocardial infarction or stroke [40]. Also, the difference in the occurrence of the primary endpoint appeared too early in the study [40,41]. These findings suggest that this improvement was not related to atherosclerotic change, improvement in blood pressure, or glucose control but might be related to the hemodynamic effects associated with the SGLT2 inhibitor [41].

EMPA-REG OUTCOME is the first CV safety trial to show improved CV outcome in high-risk patients. Although, in PROactive and IRIS trials, pioglitazone demonstrated CV benefit in patients with type 2 diabetes at high CV risk, there remains a major concern about the increase in heart failure associated with pioglitazone treatment [22,23]. Recently, other CV safety studies with diabetes drugs including DPP-4 inhibitor or GLP-1 receptor agonist have shown only neutrality, not superiority, with regard to CV outcome [25-27,38].

EMPA-REG OUTCOME is the only trial to examine the effects of an SGLT2 inhibitor on CV events, making it difficult to draw any conclusion on the CV effects of other SGLT2 inhibitors [41]. A number of other SGLT2 inhibitor CV safety studies (DECLARE-TIMI58 [Dapagliflozin Effect on Cardiovascular Events-Thrombolysis In Myocardial Infarction 58], Clinical Trial.gov number, NCT01730534; CANVAS [Canagliflozin Cardiovascular Assessment Study], NCT01032629) are ongoing [42]; their results are expected to conclude whether the effects seen with empagliflozin are class effects of the SGLT2 inhibitor.

CONCLUSIONS

The rosiglitazone experience aroused awareness of potential CV risk associated with diabetes drugs and prompted the FDA to issue new guidelines about CV risk [10,20]. Through post-marketing CV safety trials, some drugs have demonstrated CV benefits, while some anti-diabetic drugs raised concern about a possible increased CV risk associated with drug use [23,24,28,31,40]. Patients with diabetes have various clinical presentations, different courses of disease, and different responses to therapeutic agents, which emphasize the need for individualized and patient-centered care [43]. With the development of new classes of drugs, treatment options became wider, and the complexity of glycemic management in type 2 diabetes has increased [44]. Thus, when choosing the appropriate treatment strategy in patients with type 2 diabetes at high CV risk, not only the glucose-lowering effects, but also the overall benefits and risks of CV disease should be taken into consideration.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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