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Antidiabetic Treatments and Cardiovascular Implications

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The incidence of diabetes among Oregon Health Plan (OHP) members is approximately 19%, costing $106 million dollars on an annual basis.[1] A major contributor to the morbidity of these patients is the high incidence of cardiovascular disease (CVD).[2] Improving glycemic control has been shown to have microvascular benefits, but evidence of macrovascular benefits (e.g., cardiovascular [CV] outcomes) remain scarce. This newsletter will review the potential CV effects associated with the most common diabetes medications.

Metformin

The beneficial CV effects of metformin have been debated in the literature. The original data suggesting positive CV outcomes with metformin came from the United Kingdom Prospective Diabetes Study (UKPDS) in 1998.[3] The UKPDS trial showed a 16% reduction in CVD events (combined fatal or nonfatal MI and sudden death) in the intensive glycemic control arm that did not reach statistical significance.[3] After 10 years of follow-up, those originally randomly assigned to intensive glycemic control with metformin had significant long term reductions in myocardial infarction (MI) (Risk Ratio [RR] 0.67; 95% CI 0.51-0.89; ARR 6.3%; number needed to treat [NNT] 16) and a 7% absolute reduction in all-cause mortality (NNT 14) compared to the conventional glycemic control group.[4] Conversely, a systematic review evaluated the non-UKPDS metformin monotherapy trials and showed no significant benefit on mortality (RR 2.94; 95% CI 0.31-28.16) or ischemic heart outcomes (RR 3.02; 95% CI 0.62-14.75).[5] Additionally, the ACCORD trial suggested a possibility of increased all-cause mortality in the intensive arm, in which approximately 94% of patients were on metformin therapy.[6] In conclusion, the positive CV effects associated with metformin comes from the UKPDS trial; these results have not been replicated and were likely, in part, a product of trial design. UKPDS included patients with newly-diagnosed diabetes who were largely free of vascular events, whereas the major trials that have not found a reduction in CVD outcomes with intensive glycemic control (ACCORD[6], ADVANCE[7], VADT[8]) included participants who had more advanced type 2 diabetes (T2DM). Regardless, metformin is a suitable first choice for hyperglycemic therapy based on its efficacy in lowering hemoglobin A1C (A1C), positive effect on weight, and low cost, in addition to the potential to decrease CV events when initiated early on in the disease.

Sulfonylureas

There is conflicting data suggesting that the use of sulfonylureas may be associated with an increase in CV events and mortality.[9] However, this finding is most consistent with first generation sulfonylureas that are no longer used. Overall, it is unlikely that sulfonylureas directly cause CVD, but some hypothesize that they may worsen outcomes due to the effect of sulfonylureas on mitochondrial ATP-sensitive potassium channels in cardiac myocytes.[10] In addition, sulfonylureas have a relatively high risk of hypoglycemia, which can precipitate adverse CV outcomes such as myocardial ischemia and cardiac arrhythmia.[11] There is also data supporting the relative CV safety of sulfonylureas from a systematic review comparing sulfonylurea monotherapy to placebo and other agents for the treatment of T2DM.[12] In this review, there were no significant differences in CV mortality or overall mortality between sulfonylurea monotherapy and any other class of agents. This was similar to the BARI 2D study which demonstrated no difference in CV events or mortality between those on an insulin-sensitizing regimen versus insulin-provision therapy (insulin and/or sulfonylurea) over 5 years of follow up.[13] In conclusion, there is no reason to prefer or to avoid sulfonylurea therapy based on CVD considerations but patients and providers should be aware of the potential CV risks of hypoglycemia in patients with underlying CVD.

Insulin

The use of insulin is known to be a potent glucose lowering agent but the CV effects have been inconclusive. Recently, the ORGIN trial compared glargine to standard of care (predominately metformin and sulfonylureas) and found glargine to have a neutral effect on CV outcomes (hazard ratio [HR] 1.02; 95% CI, 0.94 to 1.11).[14] A CV study comparing degludec to glargine will have results in September of 2015, which will help to further define the relationship between insulin and CVD.[15]

Thiazolidinediones

Historically, the thiazolidinediones (TZDs), especially rosiglitazone, have been viewed as having a potentially negative CV effect. A meta-analysis of rosiglitazone demonstrated an increased risk of MI (OR 1.43; 95% CI 1.03 to 1.98; P=0.03).[16] However, a review of the re-adjudicated results of the evidence found that rosiglitazone wasn't associated with an increased risk of MI compared to metformin or sulfonylureas.[17] A RCT specifically designed to assess the CV impact of pioglitazone included 5,238 patients with T2DM and macrovascular disease.[18] The primary endpoint was the composite of all-cause mortality, MI, stroke, acute coronary syndrome, coronary or leg revascularization or leg amputation. No significant difference was found between pioglitazone and placebo (HR 0.90; 95% CI, 0.8-1.02; P=0.095).[18] Other studies have shown an increased risk of heart failure (HF) with rosiglitazone and pioglitazone, supported by findings from a meta-analysis showing a hazard ratio for pioglitazone of 1.32 (95% CI, 1.04 to 1.68) and for rosiglitazone 2.18 (95% CI, 1.44 to 3.32).[19] Lack of conclusive CV benefit and side effects such as weight gain, HF and edema limit routine use of TZDs in patients with CV disease.

DPP-4 Inhibitors

The dipeptidyl peptidase-4 (DPP-4) inhibitors have CV results for three of the four approved therapies. In the EXAMINE trial, 5,380 patients with T2DM and a recent acute coronary syndrome (ACS) were randomized to alogliptin or placebo.[20] The primary endpoint was the composite of death from CV causes, nonfatal MI, or nonfatal stroke. A neutral effect was seen on CV endpoints with the primary outcome experienced by 11.3% in the alogliptin group compared to 11.8% in the placebo group (HR 0.96; P<0.001 for noninferiority).[15] Observational studies have shown CV benefit with glucose lowering, however, the lower A1C levels associated with alogliptin compared to placebo, -0.33% vs. 0.03%, did not translate into CV benefit.[20] Sitagliptin was also compared to placebo in the TECOS trial.[21] The primary composite outcome was CV death, non-fatal MI, and non-fatal stroke or hospitalization for unstable angina. After a median follow up of 3 years, sitagliptin was not associated with any CV harm or benefit compared to placebo, 11.4% vs, 11.6% (HR 0.98; 95% CI, 0.88 to 1.09; P=0.001 for noninferiority).[21] Heart failure-related hospital admissions was a secondary outcome that was also found to be the same in both groups, 3.1% (HR 1.00; 95% CI, 0.83 to 1.20; P = 0.98).[21] The CV effects of saxagliptin were studied in patients with T2DM and CVD.[22] The primary outcome was a composite of CV death, nonfatal MI, or nonfatal ischemic stroke. The incidence of the primary endpoint was 7.3% for saxagliptin vs. 7.2% for placebo after a follow-up of 2.1 years (HR 1.00; 95% CI, 0.89 to 1.12; P<0.001 for noninferiority).[22] There was an increased risk of hospitalization for HF in the saxagliptin group compared to placebo, 3.5% and 2.8%, respectively (HR 1.27; 95% CI, 1.07 to 1.51; P=0.007).[22] The mechanism for the elevated hospital admissions with saxagliptin is unknown. DPP-4 inhibitors appear to exhibit neutral CV effects, except for an increased risk of hospitalization for HF with saxagliptin, which warrants continued monitoring.

GLP-1 Receptor Agonists

Prospective, randomized trials evaluating the CV effects of glucagon-like peptide-1 (GLP-1) receptor agonists are ongoing and have not been published. In a meta-analysis of 37 trials, GLP-1 receptor agonists were compared to various treatments from other therapeutic classes in T2DM

patients.[19] GLP-1 receptor agonists were not found to be associated with an increased risk of major CV events (MACE) compared to active or placebo treatments (OR 0.78; 95% CI, 0.54 to 1.13; p=0.18).[19]

SGLT-2 Inhibitors

Recently, trial results for the CV safety of empagliflozin, 10 mg and 25 mg, were compared to placebo over a median observation time of 3.1 years in patients with T2DM and preexisting CV disease. [23] The primary composite outcome was CV death, nonfatal MI or nonfatal stroke. Pooled empagliflozin doses were shown to decrease the primary composite outcome more than placebo, 10.5% vs. 12.1% (HR 0.86; 95.02% CI, 0.74 to 0.99; P<0.001 for noninferiority and P=0.04 for superiority).[23] The difference in the primary endpoint was driven by a significantly lower incidence of CV death in the empagliflozin group: 5.9% vs. 3.7% (p<0.001). All-cause mortality was also significantly lower, 8.3% vs. 5.7% (p<0.001).[23] It has been theorized that the CV benefits could be related to diuresis caused by empagliflozin, which is supported by the decreased incidence of hospitalizations related to HF found with empagliflozin compared to placebo, 4.1% vs. 2.7% (HR 0.65, 95% CI, 0.50 to 0.85; P=0.002).[23]

Empagliflozin trial results are significant because it is the first diabetes drug to demonstrate a reduction in CV events in an adequately powered randomized controlled trial. Limitations to CV benefits seen with empagliflozin are that all included patients had preexisting CV disease and there is no evidence that these findings would apply to patients without preexisting disease. Empagliflozin should not be used in patients who have reduced kidney function and the rate of genital mycotic infections are more common with empagliflozin than in placebo treated patients.[24] Additionally, canagliflozin, another SGLT-2 inhibitor, has been shown to increase the risk of bone fractures and it is not known if this is a class effect.[25] Two CV safety and efficacy trials with canagliflozin and dapagliflozin are ongoing and will clarify effects of SGLT-2 inhibitors on CV outcomes.[26, 27]

High quality, prospective trials will provide valuable evidence to direct prescribing of antidiabetic agents. In addition to CV implications, consideration of adverse event profiles and patient characteristics should be considered so that benefits can be maximized and risks minimized.

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