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Cardiovascular safety of new drugs for the treatment of obesity and diabetes

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In the past, several anti-diabetic agents under development or already approved, including Muraglitazar, a dual peroxisome proliferator-activated receptor (PPAR) agonist and Rosiglitazone (a Thiazilidinedione) gave rise to valid concerns about adverse cardiovascular events, further enhanced by the results of the ACCORD Study in 2008.

In response to the above in July 2008, the FDA's Endocrinology and Metabolism Advisory Committee issued new industry guidelines on the assessment of cardiovascular risk of anti-diabetic agents before and after market placement. These guidelines have led to radical changes in the evaluation process for all new anti-diabetic drugs being evaluated and /or already on the market. These guidelines have led to double of the number of clinical trials of cardiovascular outcomes and a six-fold increase in the median number of patients participating in cardiovascular trials, in the first 36 months.

Epidemiological evidence suggests a close relationship between plasma glucose levels, morbidity and mortality in Type 2 Diabetes (T2D). Although many trials have shown significant benefits to micro-vascular outcomes from lowering glucose levels, no consistent data on the effects on macro-vascular events were evident.

A meta-analysis of the UKPDS, PROactive, ADVANCE, VADT and ACCORD studies demonstrated cardiovascular benefits from intensive glucose-lowering therapy. After approximately 5 years of treatment, a 0.9% decrease in HbA1c resulted in a significant reduction in non-fatal myocardial infarction and coronary heart disease and a non-significant reduction in stroke. There was no benefit in mortality reduction from all causes. Indeed, the ACCORD trial was discontinued early after 3.5 years, due to high mortality rates among participants with a HbA1c <6.0% primary target.

Therefore there is still a need for a safe and effective antidiabetic treatment that offers both glycemic control and macro-vascular benefits in T2D patients. This is a more moderate effect than the number of events prevented for each of 4 mmHg drop in blood pressure or for any decrease in LDL cholesterol. This demonstrates the importance of a multi-intervention approach in the treatment of T2D patients to reduce cardiovascular risk.

With regards to Metformin and CV outcomes related to its prescription, the UKPDS study (1998) provides evidence for the beneficial CV effects of metformin. In the UKPDS 34 study, the metformin group had a 39% lower risk of myocardial infarction (MI) than the conventional treatment group ($p = 0.01$). The significant reduction in MI risk endured for over 10 years. Metformin added to Sulphonylurea (SU) vs SU alone, was associated with increased risk of diabetes-related death (RR of 1.96, $p = 0.039$) and all-cause mortality (RR of 1.60 $p = 0.041$). In the UKPDS 34 study, overweight patients treated with metformin had reduced risk for any diabetes-related endpoint, diabetes-related death and all-cause mortality.

The PROactive study demonstrated that pioglitazone was not significantly superior to placebo for the primary endpoint, which was the composite of all-cause mortality, non-fatal MI (including silent MI), stroke, acute coronary syndrome (ACS), endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. However, pioglitazone was significantly superior to placebo for the secondary endpoint key, which was the composite of all-cause mortality, non-fatal MI and stroke.

Studies on ddp4 inhibitors (TECOS, EXAMINE, SAVOR-TIMI, CAROLINA, CARMELINA) demonstrated cardiovascular safety but not superiority, and in the case of saxagliptin (SAVOR-TIMI) increased risk of hospitalization for heart failure.

The most significant results were seen in the Sodium-glucose co-transporter-2 (SGLT2) inhibitors category, where studies (EMPAREG, CAMVAS, DECLARE-TIMI) showed not only safety but in many drugs, significant benefits for cardiovascular, renal symptoms and heart failure symptom management opening new paths of scientific enquiry.

Glucagon-like peptide 1 (GLP-1) receptor agonists Liraglutide, Semaglutide and Dulaglutide (LEADER, SUSTAIN, REWIND) studies showed significant benefits in reducing CV and renal events while other studies for drugs in same category demonstrated their safety (ELIXA, EXCEL). Newer insulins have also proven safe for any GLP-1 molecules that have been studied (DEVOTE).

In direct contrast to the CV related anti-diabetic studies, obesity related research has not shown the same progress. Many anti-obesity agents were withdrawn and those that are still available come with important safety warnings. With the possible exception of Liraglutide (approved for medical use in Europe in 2009 and in the United States in 2010) there is not much to say about cardiovascular safety for this category of agents.

In conclusion, for T2D, following the guidelines for cardiovascular safety studies, anti-diabetic agents are safe and in many cases with significant benefits for other comorbidities, while for obesity we cannot say the same as the agents currently on market do not inspire that level of safety.