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Editorial

CARDIOVASCULAR PROTECTION – THE HOLY GRAIL OF DIABETES MEDICATION ?

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Diabetes remains one of the major health issues confronting modern societies, with mean prevalence rates around 9% and almost half of billion of patients affected worldwide [1]. It is expected that this figures will rise to 10.5% prevalence and 642 million patients by 2040. The huge costs related to this disease are associated mainly with the chronic complications of diabetes, both micro and macrovascular. By far the atherosclerotic cardiovascular disease (CVD) represents the main cause of morbidity and increased mortality in patients with type 2 diabetes (T2D) [2]. There is evidence that multi-factorial treatment of T2D, including control of blood glucose, lipids and blood pressure values is associated with a significant decrease in the prevalence of cardiovascular (CV) complications and CV mortality [3]. However, the "mega-trials" comparing the efficacy of glycemic control alone (intensive vs. standard control of blood glucose values), including the ACCORD, ADVANCE and VADT trials [4-6] failed to show any benefit in T2D patients with long standing diabetes and high CV risk, at least during the randomized period of the study (with a mean follow-up of 3.5-5.5 years).

As for individual diabetes drugs, ever since the positive results obtained with metformin in the UKPDS study almost 20 years ago [7], diabetologists have continuously searched and hoped to find a drug able to actually reduce the incidence of CVD and CV death in T2D patients. In the last 8 years, after the U.S. Food and Drug Administration (FDA) requested that all new diabetes drugs prove at least cardiovascular safety in order to maintain their marketing authorization (with an upper bound of the two-sided 95 percent CI for the estimated risk ratio lower than 1.3.), a lot of large scale CV endpoint trials have been initiated [8]. Unfortunately, year after year and study after study, pioglitazone, different dipeptidyl peptidase 4 (DPP-4) inhibitors (alogliptin, saxagliptin and sitagliptin) and glucagon like peptide 1 receptor agonists (GLP-1RA) (lixisenatide), though proving CV safety, failed to bring definite benefits in CV risk reduction.

When all hopes were lost, things changed for the better one year ago with the publication in September 2015 of the results of the EMPA-REG OUTCOME trial [9]. This was a CV safety trial testing empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor (the first CV

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study with this class of drugs to report its results). A total of 7020 subjects with T2D and established CV disease (thus a priori with very high risk) were included in the study and followed-up for a median time of 3.1 years. They were randomized in three intervention groups: EMPA 10 mg, EMPA 25 mg and placebo, all added to standard of care treatment. Similar with the majority of the latest trials (and in accordance with the FDA recommendations), the primary outcome – major adverse cardiovascular event (MACE) was a composite of CV death, nonfatal myocardial infarction (MI) or nonfatal stroke. Patients had a mean age of ~63 years, rather moderate metabolic control (HbA1c ~8%) and usually diabetes for more than 10 years [9]. Around 10% of patients had a previous diagnosis of heart failure, an issue more and more important in the continuum of care of T2D subjects. In the end, EMPA treated patients had a significant (p - 0.04) 14% reduction of the relative risk for the primary composite endpoint (MACE). Analysis of the individual components of this endpoint indicated that the reduction was driven mainly by a spectacular reduction with 38% of CV death (p<0.0001) while there were non-significant changes in nonfatal MI and nonfatal stroke. Analysis of secondary outcomes showed also a spectacular reduction with 32% of all-cause mortality and with 35% of hospitalizations for heart failure [9].

Very interestingly, all the positive CV effects occurred early in the trial and continued throughout it. There is intense debate regarding the possible mechanisms explaining the results in EMPA-REG. The speed of CV protection appearance rules out an important contribution of glycemic control, weight loss and even blood pressure reduction. Overall, it seems it could not possibly be due to a reduction in atherosclerosis or even a slowing down of atherogenesis [10]. Putative mechanisms involved could be volume depletion with increase in hematocrit, the diuretic effect and possible antiarrhytmic effect. More recently [10], a hypothesis emerged regarding the metabolic effects of glycosuria associated with empagliflozin use and its consequence of moderate rise in ketonemia. The hypothesis suggests that the mild increase in beta-hydroxybutyrate provides a "super fuel" to peripheral tissues, including the heart and the kidney. This can be taken up freely in a non-insulin dependent manner by these tissues. Moreover, metabolization of beta-hydroxybutyrate requires less oxygen than in the case of glucose, increasing the amount of adenosine triphosphate (ATP) produced in the presence of reduced oxygen flow in the tissue [10].

More recently, other data from the EMPA-REG OUTCOME trial showed that treatment with empagliflozin in that group of high CV risk T2D subjects was associated with a decrease of the progression of chronic kidney disease as well as of the frequency of significant renal events, indicating a degree of renal protection [11]. It remains to be seen if future CV outcome trials using other drugs of the SGLT2i class – DECLARE-TIMI 58 (dapagliflozin), CANVAS (canagliflozin) and VERTIS-CVO (ertugliflozin) will confirm the results of the EMPA-REG OUTCOME trial, indicating a class-effect of CV and renal protection.

This summer, results of the LEADER trial (the CV outcome study using liraglutide, an once daily GLP-1RA) were presented during the American Diabetes Association meeting in New Orleans, and simultaneously published in NEJM [12]. This study begun in 2010 and randomized 9340 T2D subjects with high CV risk that were followed-up for a mean duration of 3.8 years (between 3.5 and 5 years). Subjects had a mean age at baseline of 64 years, mean disease duration of 13 years, and a HbA1c of 8.7%

(rather poorly controlled diabetes). Subjects received either s.c. liraglutide or placebo, added to standard of care treatment. The primary outcome was again MACE, with the composite of CV death, nonfatal MI or nonfatal stroke. At the end of the follow-up period, patients treated with liraglutide exhibited a significant (p – 0.01) 13% reduction of MACE compared to placebo treated patients. Similar with the results in EMPA-REG trial, subjects treated with liraglutide exhibited also a 22% reduction of CV death (p=0.007) and 15% reduction in all-cause mortality (p=0.02) [12]. Liraglutide also reduced HbA1c, body weight, and had a low risk of hypoglycemia. Its safety profile was similar to what has been seen in previous trials for glycemic control, gastrointestinal events and increases in heart rate being the most common.

There was similitude but also important differences when comparing LEADER with EMPA-REG OUTCOME data, namely only a non significant reduction of hospitalization for heart failure with liraglutide and the speed of the CV protective effect. Thus, the two curves in the Kaplan-Mayer plot started to diverge more slowly, usually after 12-18 months of treatment. This suggests that the mechanism of cardioprotection is different with liraglutide, authors suggesting that the observed benefits are perhaps related to the modified progression of atherosclerotic vascular disease [12].

It also remains to be seen if other GLP-1 RA CV outcome trials will confirm the effect of liraglutide in LEADER. A press statement from Novo Nordisk indicated that at least semaglutide (an once weekly injectable long acting GLP-1 RA) proved CV protection in the SUSTAIN-6 study, results that will be communicated during the EASD meeting in Munchen, September 2016 [13]. This would suggest a class effect, at least for the long acting GLP1s. However, other data are awaited from similar studies with QW exenatide (EXSCEL, 2018), dulaglutide (REWIND 2019) and albiglutide (HARMONY 2019).

So maybe the “holy grail” of CV protection with diabetes drugs is now within our reach. Of course, there is the issue of cost (both SGLT2i and GLP-1RA are new and expensive medications) and careful cost/benefit analyses should be done to elucidate the issue of the real benefit of the treatment. However, both EMPA-REG OUTCOME and LEADER trials as well as the future trials to publish their results will probably impact the regulatory agencies' and the professional societies' recommendations in a not very remote future.

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