The impact of cardiovascular outcome trials in type 2 diabetes

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Abstract

Context : Type 2 diabetes mellitus (T2DM) is one of the most challenging diseases of the 21st century, with a rapid increase in prevalence (worldwide one out of 11 patients) and accompanying healthcare costs (USD 727 billion in 2017). The increased cardiovascular (CV) risk with T2DM is well recognised, and atherosclerotic heart disease, stroke, peripheral vascular disease, and heart failure account in large part for the excess death rate. Therefore, it is of the greatest importance that antidiabetic medication is safe in terms of CV outcome, or even shows a clinically relevant CV benefit, which has been assessed in cardiovascular outcome trials (CVOTs). In the last few years, there has been an abundance of these trials, since developments in antidiabetics are rapidly progressing. The most recent drug class, the SGLT-2 inhibitors, have caused a stir in the treatment algorithm of T2DM, because of the overwhelming results of the EMPA-REG Outcome trial, lowering CV complications in CV high-risk patients. But how does this relate to the other antidiabetic drugs? To what extent should this influence the prescription policy in current practice ?

Research question : Is the published effect on CV risk with SGLT-2 inhibitors truly as overwhelming as claimed? How does this compare to other antidiabetic drugs (excluding insulin)?

Methodology : Based on the PICO-model, we did a systematic literature search in the *Web of Science* and *Pubmed* database, and selected the available CVOTs (RCTs) for all antidiabetic drugs (excluding insulin).

Results : The earliest CVOTs date back to the 1970s, with the UKPDS showing a risk reduction in mortality with metformin, but without a clear statistical benefit in terms of CV outcome, and a neutral CV outcome with sulphonylurea, however, in recent onset diabetes with low CV risk. The follow-up study of this trial, however, suggests a CV benefit through a "legacy effect" of early glycaemic control. More recent trials therefore included T2DM patients with CV high-risk. Thiazolidinediones provided the next CVOTs; despite lowering the composite of a 3-point MACE in the PROactive trial and protective cerebrovascular effects in the IRIS trial, thiazolidinediones keep being looked upon with suspicion by Belgian physicians following the suggestion of increased CV mortality risk with rosiglitazone, which were later refuted by the RECORD trial. In our opinion, this outcome shows more than non-inferiority in patients without prior documented heart failure, and the beneficial effects of pioglitazone on CV outcome is comparable to that of liraglutide (LEADER trial) and even to empagliflozin (EMPA-REG Outcome trial) and canagliflozin (CANVAS Program), all of which had a reduction in a 3-point MACE. Liraglutide and empagliflozin even had a reduction in CV mortality, which lead to the indication of using them to lower macrovascular complications in CV high-risk diabetic patients. This has changed the current treatment recommendations. Nonetheless, we take the opportunity to put the EMPA-REG Outcomes into perspective as well and address some nuances which might mitigate the magnitude of the claims, such as the high discontinuation rate of the drug (25%), the rapid decrease in cohort size despite the unchanged quantitative label of the CV risk reduction, the lack of a prespecified minimum time of follow-up, and finally the loss of superiority when 40% of presumed CV deaths, who were actually non-assessable, were excluded.

We also address the general limitations of CVOTs: 1.There is a lack of generalisability to all diabetic patients; 2.There are different patient selection criteria making them more difficult to compare; 3.There is a short time of follow-up, while CV outcomes generally are long-term processes; 4.There are only placebo-controlled trials, while head-to-head comparisons could be complementary, comparing a drug to a golden standard; 5.There are no standardised definitions of important outcomes; 6.There is disproportionate use of standard-of-care therapy in the placebo groups, which could lead to over- or underestimation of any risks or benefits.

Conclusion and recommendations : Pioglitazone, liraglutide, empagliflozin and canagliflozin are drugs of interest when it comes to lowering CV risk in T2DM. The alleged superiority of empagliflozin is questionable and we would recommend keeping the above-mentioned limitations into account when choosing anti-diabetic drugs, even in the context of current treatment guidelines. We would encourage tailoring the choice of medication to the patient, including possible pleiotropic drug effects, as well as costs, given the high and ever increasing prevalence of type 2 diabetes mellitus.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is characterised by relative insulin deficiency caused by pancreatic β-cell dysfunction and/or insulin resistance in target organs (1). It is one of the most challenging diseases of the 21st century, because the global rising tide of obesity, physical inactivity, and energy-dense diets has resulted in an unprecedented increase in the number of patients. About 425 million adults have diabetes worldwide, or about one in every 11, according to the International Diabetes Federation, with type 2 diabetes accounting for around 90% of all cases. If we do not act, this number will rise up to 629 million people in 2045; this means an increase of 45%. Half of the people with diabetes do not know they have it and are at a higher risk of developing harmful and costly complications. In 2017, healthcare costs reached USD 727 billion of global healthcare expenditure dedicated to diabetes treatment and related complications. Governments worldwide are struggling to meet the cost of diabetes care and the financial burden will continue to expand due to the growing number of people developing diabetes (2). Given the heavy economic burden on public health as well as socio-economic development, prevention of diabetes is a priority.

Diabetes is associated with numerous micro- and macrovascular complications. The benefits of intensive glucose management on microvascular complications, such as retinopathy, nephropathy, and neuropathy, have been shown in several large randomised controlled trials (RCTs) (3-7), but evidence that intensive glucose reduction reduces macrovascular outcomes, such as cardiovascular disease (CVD) and stroke, is less well established in type 2 diabetes. Current studies show a clear demonstration of a benefit of glycaemic control on CVD in type 1 diabetes (8), but demonstration of such an effect with trials in T2DM has been elusive. The UKPDS trial reduces risk for myocardial infarction by 16% (P=0.06) with lower glycaemia, but recruited a relatively young population with new-onset diabetes. These results were supported by two meta-analyses indicating a modestly reduced risk of nonfatal myocardial infarction (HR respectively 0.85 [0.76-0.94] and 0.83 [0.75-0.93]) (9, 10). In contrast, the ACCORD Study Group showed no significant reduction in major CV events in relation to HbA1c in type 2 diabetic patients with either established CV disease or additional CV risk factors (11), and the ADVANCE trial shows similar results (7).

However, cardiovascular disease remains the greatest cause of morbidity and mortality associated with T2DM (2). In a meta-analysis of nearly 700,000 people, diabetes was associated with increased risk of coronary heart disease (hazard ratio [HR] 2.00; 95% CI 1.83-2.19), ischaemic stroke (HR 2.27; 95% CI 1.95-2.65), and other deaths related to vascular disease (HR 1.73; 95% CI 1.51-1.98) (1). Intensive control of glycaemia, lipidemia and blood pressure is required in order to minimise the risk of complications and disease progression (1). It is therefore important for a general practitioner to screen for diabetes, hypertension and hypercholesterolemia, and to treat accordingly. Dietary advice, daily exercise and smoking cessation are essential; however, often administration of antidiabetic drugs are necessary in T2DM, but, as with any other medication, antidiabetic drugs can have adverse effects as well.

In 2007 there was a serious controversy regarding the thiazolidinedione rosiglitazone when a meta-analysis from 42 RCTs showed the odds ratio (OR) for cardiovascular mortality in the rosiglitazone group was 1.64 (95% CI 0.98-2.74, P=0.06) (12). Initially, the US Food and Drug Administration (FDA) issued a restriction against using rosiglitazone, but this was removed after the RECORD trial data in 2013 showed no significant increase in cardiovascular events (13). Nevertheless, the damage had

already been done: thiazolidinediones were looked upon with suspicion ever since and have failed to regain the trust of prescribing physicians. In addition, the FDA demanded post-marketing surveillance regarding cardiovascular harm or safety for all new antidiabetic drugs.

Hence, several large RCTs have since been completed to assess the cardiovascular safety of antidiabetic drugs as add-on therapy to normal standard T2DM care, and many other RCTs are still ongoing. To date, some, but not all RCTs do not manage to show more than cardiovascular safety, even when most are designed with enough power to prove superiority. However, follow-up time mostly does not exceed 3-5 years and one might wonder whether this is long enough to exclude or demonstrate a probable benefit of a study. Cardiovascular complications are long-term outcomes after all, and 3 years might not be indicative of developments on longer term, including adverse events.

Obviously, pharmaceutical firms wanted to reassure their product was safe and continue production without further delay. However, since T2DM is associated with high risk of cardiovascular death, there would be a marked added value if not only safety, but also cardiovascular risk reduction could be proven for medication, and even more so if these were independent of glycaemic control. In this regard, the PROactive (14), LEADER (15), EMPA-REG Outcome (16) and CANVAS trial (17) showed promising results on pioglitazone, liraglutide, empagliflozin and canagliflozin respectively. They have suggested superiority on cardiovascular outcome, despite possible adverse events, and this had led to new discussions and a reshuffling of treatment guidelines.

Nevertheless, the PROactive trial, is often (in our opinion) wrongly seen as a non-inferiority trial which currently stands in sharp contrast to the recent outburst of enthusiasm among diabetes healthcare professionals after the reduction in CV mortality in the EMPA-REG Outcome trial. Consequently, empagliflozin was the first and liraglutide the second antidiabetic agent to have been approved by the FDA to reduce CV complications in type 2 diabetic patients with cardiovascular disease, and the European Society of Cardiology even recommends the use of empagliflozin in patients with T2DM for the management of heart failure (18).

However, in our opinion, several nuances should be taken in consideration in the interpretation of the EMPA-REG Outcome and LEADER date, especially concerning quantitative statements regarding empagliflozin especially. Putting all cardiovascular outcome trials (CVOTs) into perspective raised some concerns regarding the set-up and interpretation of the trials. We would also like to examine to what extent these trial results can be extrapolated to the general diabetic population. When treating diabetes, we have to take into account patient characteristics (e.g. hypoglycaemic risk, weight, compliance) and drug side effects, as well as costs, guiding us through the treatment algorithm.

In the following thesis, we will discuss CVOTs available for all antidiabetic drugs, with the exception of insulin, aiming to put recent developments into perspective. What do we know today ? Which trials affected cardiovascular outcomes? What are our concerns ? What are the consequences for the future?

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2. Methodology

We used the PICO-model to do a systematic literature search.

Patient: CV high-risk patients with type 2 diabetes
Intervention: drug of interest
Comparison: placebo
Outcome: cardiovascular mortality and morbidity

A *Web of Science* and *MEDLINE/PubMed* search was done with the following MeSH terms "diabetes mellitus, type 2/drug therapy" and "myocardial infarction" or "cardiovascular disease/mortality" in combination with all of the antidiabetic drugs currently available, with the exception of insulin. We selected only randomized controlled trials and sorted by "best match". The eligible articles were selected. Furthermore, when we needed additional information, a search through the articles citing the selected RCTs was done initially. If that was insufficient, we searched for other article types such as reviews and meta-analysis regarding the drug of interest, with the same search terms. The abstracts were screened and the eligible article was included.

3. Results

3.1 FDA regulation

In 2008, the FDA provided guidance on risk assessment in order to establish the safety of new antihyperglycaemic medication to treat T2DM. Patient selection should thereby focus on patients with a higher risk of CV events (e.g. patients with advanced CV disease, elderly patients, and patients with impaired renal function), and the trials would have to include at least 2 years of CV safety data.

Furthermore, there are some statistical hurdles in the methodology of the CVOTs, before a drug can be approved (as shown in figure 1) (19, 20):

- If the upper bound of the two-sided 95% CI for HR is <1.3 and the overall risk-benefit analysis supports approval, a post-marketing CV trial may not be needed
- If the upper bound of the two-sided 95% CI for HR is between 1.3 and 1.8, a post-marketing trial will be required to definitely assess whether the upper bound is <1.3 before obtaining approval
- If the upper bound of the two-sided 95% CI for HR is >1.8, the drug is not approvable.

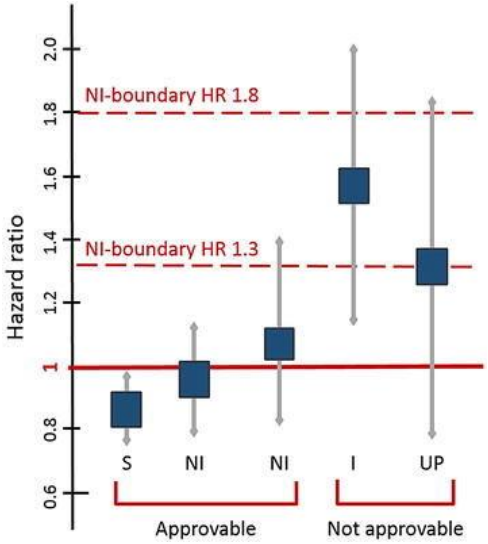


Fig. 1: Confidence interval (CI) bars indicated by FDA guideline. Five examples of hazard ratios (HR) and the upper limit of the 95 % CI of a development plan and regulatory consequence of each outcome are shown (21) .
S superiority, *NI* non-inferiority, *I* inferiority, *UP* underpowered

Cardiovascular event analysis might include a meta-analysis of all placebo-controlled trials, or an additional CVOT can be conducted. A prospective, independent adjudication of CV events in phase 2 and 3 studies must also be performed. These events include CV mortality, myocardial infarction (MI) and stroke, and possibly hospitalisation for acute coronary syndrome (ACS), urgent revascularisation and other end-points (19).

Several studies have shown that there is a correlation between HbA1c and microvascular complications of T2DM (3-7). For type 1 diabetes, there is a clear demonstration of a benefit of glycaemic control on CV disease as well (8). Such an effect has not yet been demonstrated in T2DM, with the exception of the UKPDS trial (see below). The ACCORD and ADVANCE trial show no correlation (7, 11). However, to avoid confounding results in relation to glycaemia, CVOTs starting after the above-mentioned FDA guidelines, have focused on maintaining glycaemic equipoise, generally in context of standard diabetes care (21).

3.2 Biguanides

Metformin is the only biguanide still available. The CVOTs available date back to the 1970s, with the UKPDS trial showing a decrease in mortality with metformin, compared to diet alone, in overweight patients with type 2 diabetes. Ever since, and because of its glycaemic efficacy, absence of weight gain and hypoglycaemia, general tolerability, and favourable cost, it has been the first-line treatment in type 2 diabetes, unless specifically contraindicated.

3.2.1. Mechanism of action

Metformin decreases hepatic glucose output by inhibiting gluconeogenesis. It was believed that in addition, it increases insulin-mediated glucose utilisation in peripheral tissues (such as muscle and liver), particularly after meals, and has an antilipolytic effect that lowers serum free fatty acid concentrations, thereby reducing substrate availability for gluconeogenesis. As a result of the improvement in glycaemic control, serum insulin concentrations would decline slightly (22). However, this mechanism of action is still the subject of discussion (23).

Metformin has also been shown to decrease food intake and possibly body weight (22), but it is more likely to be weight-neutral. In case of the UKPDS trial, changes in body weight were similar in the group receiving metformin versus only dietary advice, and were less than the increase in body weight observed in patients assigned intensive control with SU or insulin (4).

Unfortunately, metformin has considerable relevant side effects, most commonly consisting of abdominal discomfort, nausea and diarrhoea. These symptoms are often transient, and reversible after dose reduction or discontinuation, but remain present relatively frequent, leading to suboptimal dosage or discontinuation of the drug in a relevant number of cases.

Moreover, metformin reduces intestinal absorption of vitamin B12 in up to 30% of patients, causing vitamin B12 deficiency in 5 to 10%, but only rarely megaloblastic anaemia (27). Lactic acidosis may occur in the presence of predisposing factors, such as impaired renal function (eGFR<30ml/min), liver disease, alcohol abuse, heart failure at risk of hypoperfusion and hypoxemia, past history of lactic acidosis during metformin therapy and decreased tissue perfusion or hemodynamic instability due to infection or other cause (22).

3.2.2. Cardiovascular outcome

The first trial assessing CV outcomes with antidiabetic drugs was carried out in 1970 by the University Group Diabetes Program (UGDP) (24), but was interrupted prematurely as all oral drugs (i.a. phenformin) seemed to increase CV risk in comparison to placebo or insulin. However, this trial was underpowered and therefore the results often contested (21). The first completed trial assessing CV outcome was the 1977 UK Prospective Diabetes Study (UKPDS) (3, 4), following patients for more than 10 years. It was designed to investigate the role of glycaemic control on the complications of T2DM in newly diagnosed patients, but they found no significant reduction in macrovascular disease with more intensive treatment (insulin, sulphonylurea or metformin compared to diet alone). However, the P-value of 0.06 could suggest the possibility of a CV benefit with lower HbA1c.

A subset of 753 overweight patients was included in a separate treatment arm, showing a reduction in diabetes-related and all-cause mortality by 42% (P=0.017) and 36% (P=0.011) respectively, in favour of metformin compared to isolated diet intervention. Since the trial showed a possible benefit with greater glycaemic control, a secondary analysis compared 342 patients receiving metformin to

951 patients receiving SU or insulin, with a greater effect upon any diabetes-related endpoint (P=0.0034) and stroke (P=0.032) favouring metformin. In conclusion, the risk reduction in the primary analysis likely resulted from metformin administration as such (4).

During the 17-year post-interventional observational study of the UKPDS, significant reductions in macrovascular complications emerged in subjects who were initially assigned to antidiabetic drugs compared to diet alone. There were fewer overall deaths (RRs 0.87, 95% CI 0.79-0.96 and 0.73, 95% CI 0.59-0.89), diabetes related-deaths (RRs 0.83, 95% CI 0.73-0.96 and 0.70, 95% CI 0.53-0.92) and MI (RRs 0.85, 95% CI 0.74-0.97 and 0.67, 95% CI 0.51-0.89) in subjects who were initially assigned to intensive treatment with SU-insulin or metformin respectively. These results suggest a "legacy effect", indicating that a sustained period of glycaemic control (10 years) in newly diagnosed patients with T2DM has a long-term benefit in reducing CV morbidity and mortality (25).

A meta-analysis of 13 RCTs using metformin (versus placebo, diet or add-on therapy) showed that metformin did not significantly affect the primary outcome of all-cause mortality and CV mortality. The secondary outcomes (MI, stroke, heart failure, peripheral vascular disease, leg amputations, microvascular complications) were also unaffected. The end-point definitions referred to what was reported in the originally published papers, but were not available for all studies included in this meta-analysis. Therefore, the evaluation was not always based on the overall study population. Moreover, there was significant heterogeneity for the primary outcomes. Exclusion of the UKPDS trial had no effect on the primary outcomes, but the heterogeneity disappeared. There was no heterogeneity among the trials for the secondary end points (26). However, the event rate was very low and the findings should be cautiously interpreted. It is not possible to exclude the possibility that metformin causes a significant reduction in CV mortality.

Given that a large number of patients take metformin for many years as a first-line treatment for diabetes, further studies are urgently needed to clarify this situation. The ongoing Glucose Lowering In Non-diabetic hyperglycaemia Trial (GLINT) will examine the effects of metformin on CV outcomes in subjects with high CV risk and non-diabetes hyperglycaemia (27). It is a start, but similar trials are needed in type 2 diabetic patients.

3.3 Sulphonylureas and meglitinides

Sulphonylureas (SUs) are among the most widely used drugs for the treatment of patients with T2DM, while repaglinide, the only meglitinide available in Belgium, is only given in case of intolerance to SU. Although they are pharmacologically distinct, their mechanism of action is similar, and therefore they are discussed together. They work by stimulating insulin secretion and are therefore only useful in patients with some residual beta cell function. Little is known about their CV outcome, and moreover, there are no CVOTs concerning meglitinides.

3.3.1. Mechanism of action

First-generation SUs are not commonly used, owing to their long duration of action, increased risk for hypoglycaemia and the increased CV risk suggested in the UGDP (24). They are not available in Belgium. Glipizide, glibenclamide, gliclazide, glimepiride and gliquidone are so-called second-generation SUs. They have structural characteristics that allow them to be given in much lower doses than the first-generation. Nevertheless, the different SUs are equally effective in lowering blood glucose concentrations. There are, however, differences in absorption and metabolism, as well as in effective dose (28).

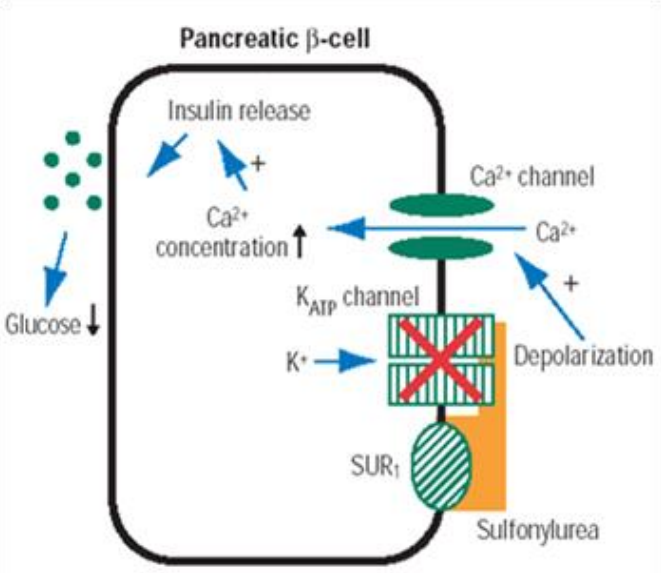


Fig. 2 : mechanism of action of SU (29)

SU binds a pancreatic beta cell receptor, that is part of the ATP-sensitive potassium (K+) channel (see figure 2 (29)). The binding leads to inhibition of the channel, which alters the resting potential of the cell, leading to calcium influx and stimulation of insulin secretion (28).

Meglitinides exert their effect through different pancreatic beta cell receptors, but in a similar way. It has a rapid onset and short duration of action, which makes it suitable for reducing postprandial hyperglycaemia (28).

Since insulin is being released independently of blood glucose concentrations, there is a substantial risk of hypoglycaemia with SU. It is the most common side effect and patients should be cautioned in situations in which hypoglycaemia is most likely to occur, such as after exercise or a missed meal, in patients who are undernourished or abuse alcohol, in patients with impaired renal or cardiac function or gastrointestinal disease, with concurrent therapy with sulfonamides or fibric acid derivative, or after being in the hospital (28). In the UKPDS trial, there were more hypoglycaemic episodes in the intensive group, as well as more weight gain (3), which is again related to the increased insulin secretion. Repaglinide has a similar risk for weight gain, but possibly lower risk of hypoglycaemia, and is completely metabolised in the liver. Therefore, it can safely be administrated in case of decreased renal function (28).

3.3.2. Cardiovascular outcome

There are no long-term studies of meglitinides to assess CV outcomes or mortality in patients with T2DM. Consequently, whether meglitinides are associated with poorer outcomes in patients who have had a myocardial infarction is not known.

Concerning SUs, however, it was the UGDP showing an increased risk of CV mortality with tolbutamide (24). It was not until the UKPDS trial (3) that another RCT assessed CV outcome of SUs again. They included 3867 non-overweight patients, newly diagnosed with T2DM, who were randomly assigned to an intensive regiment with SU (chlorpropamide, glibenclamide or glipizide) or insulin treatment versus conventional treatment with diet alone. After nearly 11 years, the risk for any diabetes-related endpoint was 12% lower in the intensive group (P=0.029), mainly due to a decrease in microvascular disease. The risk reduction for any diabetes-related or all-cause mortality did not reach statistical significance, with no differences within the intensive policy group (3). So there was neither a CV risk or benefit, although the study lacked sufficient power to exclude a beneficial effect on fatal outcomes. A recent meta-analysis supported this CV safety (30), although they included studies with a follow-up of only 1 year and studies underpowered to assess the CV outcome. Accordingly, their safety cannot be guaranteed and further research should be done.

3.4 Thiazolidinediones

Thiazolidinediones were the incentive for the FDA to demand CVOTs after a meta-analysis with rosiglitazone suggested increased CV mortality. Although these results were refuted, one remains cautious and it is rarely a drug of choice while treating T2DM. Thiazolidinediones work by increasing insulin sensitivity through activation of peroxisome proliferator-activated receptors (PPARs), nuclear receptors which are present in a variety of tissues and organs. Fluid retention and therefore heart failure (HF) is the most feared side effect in patients who are at risk, whereas other CV pleiotropic effects, such as blood pressure lowering, vasorelaxation and left ventricular remodelling might improve CV outcome (31).

3.4.1. Mechanism of action

The thiazolidinediones lower plasma glucose among patients with T2DM through direct increase in insulin sensitivity by acting on adipose, muscle and liver to increase glucose utilisation, and decrease glucose production. They also preserve beta-cell function (32). They are direct stimulators of the ubiquitous intranuclear PPAR (see figure 3):

- PPAR-γ is found predominantly in adipose tissue, pancreatic beta cells, vascular endothelium, macrophages, and the central nervous system. It stimulates adipocyte differentiation, improves insulin sensitivity, reduces hyperglycaemia, and has shown experimental pleiotropic prevention of atherosclerosis (32).
- PPAR-α is expressed mostly in liver, heart, skeletal muscle, and vascular walls. It stimulates lipid oxidation, decreases circulating triglycerides, increases HDL-cholesterol, and has antiatherosclerotic activity (32).

Rosiglitazone is a pure PPAR-γ agonist and pioglitazone binds both PPAR-γ and some PPAR-α receptors, which might explain their different effects on lipid metabolism : both agents improve HDL-cholesterol and decrease serum free fatty acids, while only pioglitazone reduces triglycerides as well (32). Their effect on glycaemic control, however, is similar. In addition, they might have cardioprotective effects independent of glucose lowering : reduced carotid intimal medial thickness and coronary intimal hyperplasia, normalisation of vascular endothelial function, lower blood pressure, and improved fibrinolytic and coagulation parameters (31). Also, apart from vitamin E, it is the only drug class that has proven therapeutic efficacy regarding non-alcoholic steatohepatitis (NASH). Some studies even suggest a protective effect against a variety of cancers (lung, breast, colorectal) (33). However, much of the available data are based on animal models, and pioglitazone has been implicated as causing bladder cancer, although recent studies (34) and the available CVOTs (PROactive, IRIS and TOSCA.IT trial (14, 35, 36)), which will be reviewed in the next section, show no increased risk. If it is indeed associated with bladder cancer, the absolute risk to an individual is probably very small. Current recommendations to avoid its use in patients with a history of bladder cancer, however, seem prudent (37).

Other adverse effects have raised concerns as well; these effects include weight gain, fluid retention and increased risk of bone fractures. The weight gain is a result of fluid retention, possibly increased appetite, and subcutaneous (but not visceral) fat accumulation (37, 38); the selective femoral fat expansion through recruitment of young fat cells is thought to exert a protective metabolic effect. Thus, waist-to-hip ratio decreases, however without decrease in visceral fat (39). Intravascular fluid retention, however, increases the risk of symptomatic heart failure in predisposed individuals. The RECORD trial suggested an increased risk of heart failure (HF) with rosiglitazone (HR 2.10, 95% CI

1.35-3.27), which was seen as well with pioglitazone. In the PROactive trial, there was more heart failure with pioglitazone, whether or not the patient was hospitalised (6% vs 4% in placebo, HR 1.75, P<0.0001), but not with more fatal outcome (14). Unfortunately, there is a diagnostic bias, since thiazolidinedione-induced fluid retention may cause edema regardless of heart failure, but in some protocols it was nonetheless classified as such, leading to overestimation of the heart failure risk. On the other hand, the exclusion of patients with a history of HF (NYHA class II or higher) might also have underestimated HF risk. The IRIS trial did not observe a greater incidence of HF, although they excluded patients with a history of HF as well (NYHA class II with reduced ejection fraction or higher), but they used safety algorithms that triggered dose reduction for excessive weight gain or edema, which could explain the difference in HF risk compared to the PROactive trial. Remarkable is the drug discontinuation of 40%, compared to 33% of patients receiving placebo, because of this (36). The TOSCA.IT trial showed a similar outcome, with no difference in weight gain and HF in the pioglitazone group compared to sulphonylurea. They did exclude patients with HF or reduced renal function, as well use about half the maximum recommended dose. The drop-out rate was higher as well, but this was mostly due to the safety concerns raised in 2012 (35). In conclusion, thiazolidinediones should be used with caution in patients with increased HF risk and should be avoided in NYHA class III or IV, but in case of other CV history they are safe and probably advantageous to use.

Furthermore, there is increasing evidence suggesting thiazolidinediones decrease bone density and increase fracture risk, particularly in women and mainly in distal upper or lower extremities. This was confirmed by the RECORD (HR 1.57, 95% CI 1.26-1.97) (13) and IRIS trial (HR 1.53, 95% CI 1.24-1.89) (36) with rosiglitazone and pioglitazone respectively, but not by the TOSCA.IT trial (P=0.75) (37) and not reported in the PROactive trial (14). The mechanism is uncertain, but we must point out that possible effects on fractures, as well as cancer, will probably take a longer follow-up to become apparent, and that more trials are needed to effectively address the matter.

Finally, the thiazolidinedione troglitazone was removed from the market because of reports of severe hepatocellular injury (38), but this was not reported with rosiglitazone and pioglitazone. The FDA currently recommends that patients receiving either one, undergo baseline testing, followed by periodic monitoring, of liver function.

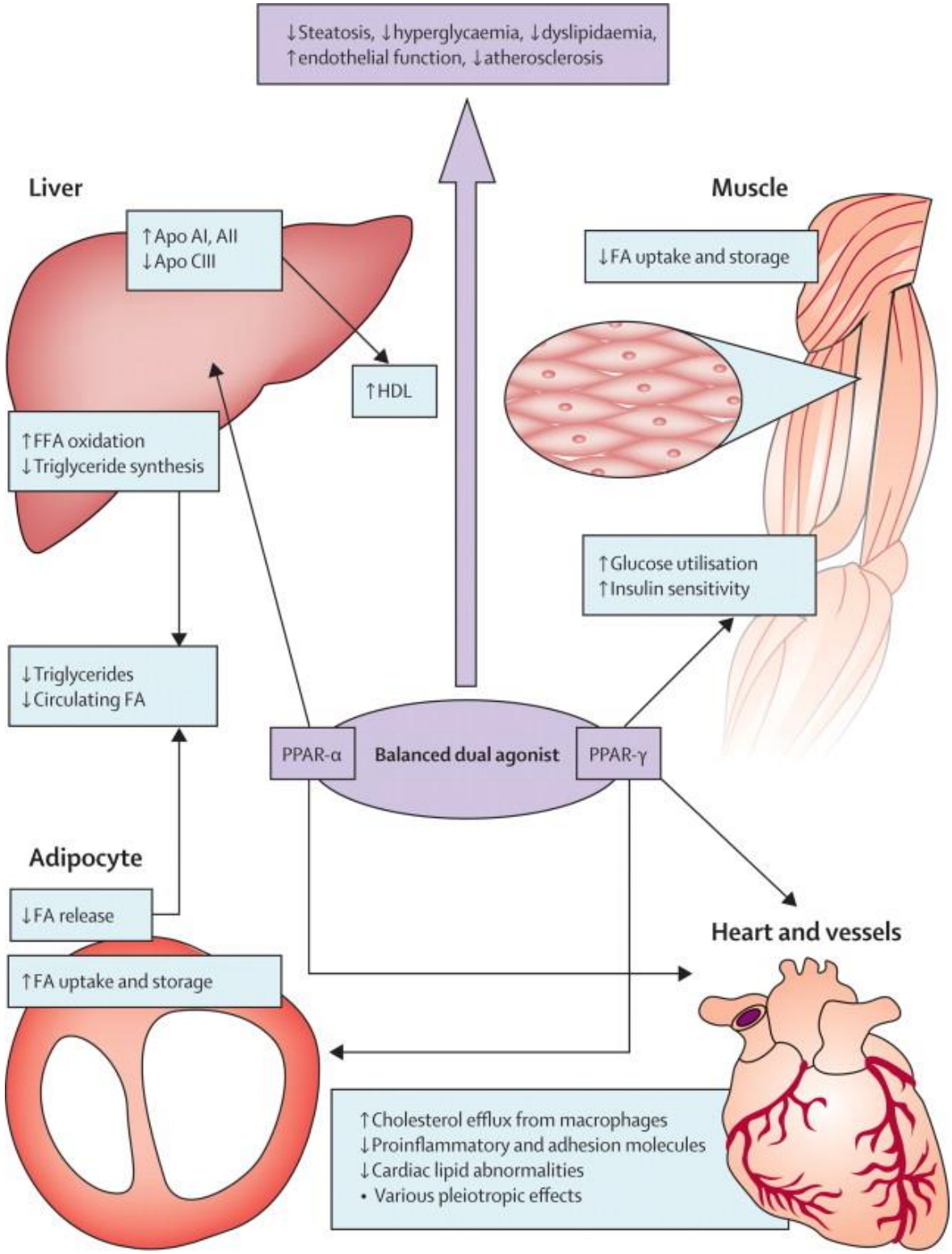


Figure 3. Synergistic beneficial actions of balanced PPAR-α/γ agonists. Apo=apolipoprotein. FA=fatty acids. FFA=free fatty acids.(32)

3.4.2. Cardiovascular outcome

As mentioned, the FDA imposed marked restrictions on the prescribing of rosiglitazone, because of concerns about increased risk of acute MI and CV death based on a retrospective analysis of 42 RCTs (12). These restrictions were largely removed in 2013 after the prospective RECORD study (13), which evaluated the effects of rosiglitazone on CV events and mortality in 4447 patients with T2DM. Patients were randomly assigned to the addition of rosiglitazone, metformin or SU to evaluate rosiglitazone effects on CV events and mortality. After a mean 5.5 years of follow-up, there was no difference in primary outcome (CV hospitalisation or CV death) between the rosiglitazone and control groups and the effect on MI was inconclusive (HR 1.14, 95% CI 0.80-1.63), but the study lacked power eventually, due to the lower event rate and higher drop-out rate (13).

The PROactive, IRIS and TOSCA.IT trial, however, found more promising effects on CV outcome with pioglitazone treatment.

The PROactive trial (14) is a RCT of 5239 patients with T2DM and evidence of macrovascular disease, with a follow-up of 2.85 years, receiving either pioglitazone or placebo. The primary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle, resulting in a 10% risk reduction, although not statistically significant (P=0.095). The secondary composite outcome (i.e. all-cause mortality, non-fatal MI and stroke) on the other hand, did show a significant risk reduction of 16% (P=0.027), while the individual components showed no statistically significant reduction (14). In addition, patients with prior myocardial infarction had a 28% risk reduction of developing a new myocardial infarction (P=0.045) (40). Cardiovascular deaths were assessed individually and were similar in both study groups, although all fatal events were classified as cardiovascular unless there was a clear non-cardiovascular cause (14). Furthermore, since the event rate was higher than anticipated and the enrolment rate was faster than planned, the study was terminated prematurely. To ensure sufficient duration of exposure however, the protocol was amended to specify that the trial should continue until every patient had been followed-up for 30 months (14).

Regarding the CV risk factors, the concentrations of HbA1c (-0.8 VS -0.3%), triglycerides (-11.4 VS -1.8%), blood pressure (-3mmHg VS 0mmHg) and LDL-to-HDL ratio (-9.5% VS -4.2%) decreased significantly more in the pioglitazone group compared to placebo (14). Apart from the cardioprotective effects of thiazolidinediones mentioned in the mechanism of action, a reduction in these CV risk factors could help to explain their possible CV benefit. Furthermore, increasing insulin sensitivity is another important factor. Since insulin resistance is a risk factor for stroke and MI, it is possible that patients with a history of one of these conditions, benefit from pioglitazone. This was first demonstrated by a post-hoc analysis of the PROactive trial (40) evaluating 2445 patients who had a previous MI. There was a significant risk reduction of fatal and nonfatal MI (HR 0.72, P=0.045) and acute coronary syndrome (HR 0.63, P=0.035) (40). The IRIS trial (36) had a similar outcome, evaluating pioglitazone as add-on therapy in 3876 patients with insulin resistance, but no diabetes, who had a recent ischemic stroke or TIA. After a follow-up of 4.8 years, there was a significant effect on primary outcome, which included fatal and nonfatal stroke or MI, with a HR of 0.76 (P=0.007). All-cause mortality however, did not differ significantly (36).

These results were partially supported by the TOSCA.IT trial (35): a randomized, pragmatic clinical trial in which patients with T2DM inadequately controlled with metformin monotherapy were assigned to either pioglitazone (n=1535) or a SU(n=1493) as add-on to metformin. They detected no difference in the incidence of any of the CV outcomes, including MI or stroke, after a median follow-up of 4.8 years (35). The reason for this discrepancy with the PROactive and IRIS trial however, might not only relate to the outcomes assessed, but also to the choice of comparator and features of the study population, because the prevalence of baseline CV disease in TOSCA.IT, as well as the rate of CV events, were low. In this low-risk population, the beneficial effects of pioglitazone on CV diseases might be too small to be detected in absolute terms. However, results of the post-hoc on-treatment analysis of the key secondary endpoint showed a significant reduction in ischaemic CV events in the pioglitazone group compared to SU (HR 0.67, P=0.03) (35).

3.4 SGLT-2 inhibitors

The sodium-glucose co-transporter (SGLT)-2 inhibitors are a new group of oral medications used for treating T2DM. Inhibition of SGLT-2 leads to the decrease in blood glucose due to the increase in renal glucose excretion. The EMPA-REG Outcome trial surprised the diabetes community by suggesting an impressive reduction in CV deaths with empagliflozin, starting within weeks of treatment. This was therefore clearly independent of diabetic control, and has led to discussions on whether diabetes practice guidelines should shift to favour empagliflozin.

3.4.1. Mechanism of action

SGLT-2 inhibitors reduce blood glucose by reducing reabsorption of intratubular glucose, and thus increasing glucosuria. SGLTs are a family of sodium-dependent glucose transport proteins, of which SGLT-2 and SGLT-1 are involved in glucose reabsorption in the kidneys (see figure 4) (41).

SGLT-1 proteins are high affinity, low capacity transporters of glucose. They are expressed in the small intestine, as well as the proximal tubule of the kidneys. SGLT-1 receptors are responsible for 10% of filtered glucose reabsorption, and inhibition of SGLT-1 may lead to gastrointestinal complications, including diarrhea. SGLT-2 proteins are also expressed in the proximal tubule of the kidneys, and are responsible for about 90% of filtered glucose reabsorption. The normal renal threshold for reabsorption of glucose corresponds to a serum glucose concentration of 180mg/dl. In patients with T2DM, this threshold can increase and expression of SGLT-2 proteins can be upregulated, causing a maladaptive response that worsens hyperglycaemia. Selective inhibition of SGLT-2 proteins reduces this threshold to as low as 40-120mg/dl and decrease renal glucose reabsorption (42).

Dapagliflozin, empagliflozin and canagliflozin are the current FDA-approved inhibitors of SGLT-2, empagliflozin having the greatest selectivity for SLGT-2 compared to SGLT-1 (2500:1) and canagliflozin the least (250:1) (43).

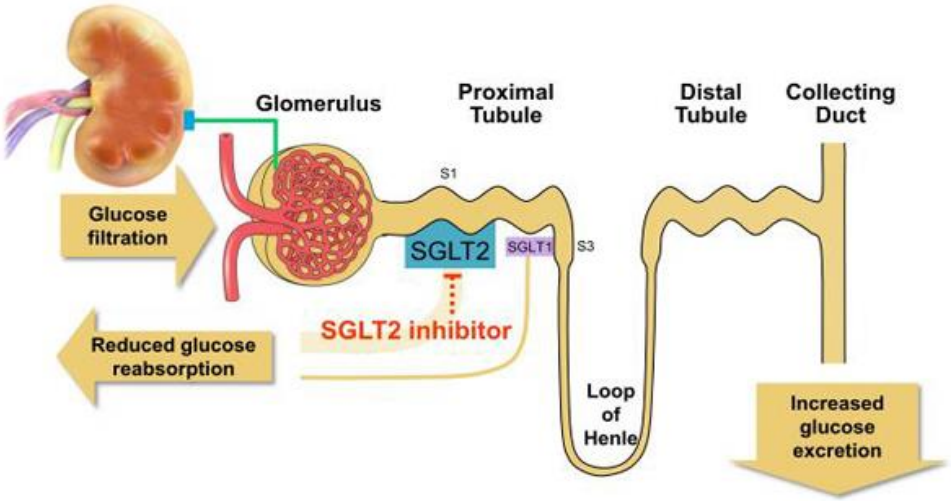


Fig. 4: mechanism of action of SGLT-2 inhibitors in the proximal tubule of the kidneys (41)

When prescribing this drug class, one has to be sure of a favourable risk-benefit profile, since there are certain adverse events that have to be taken into account.

First, predisposition to genital infections and urinary tract infections in T2DM results from several factors, such as glucosuria, adherence of bacteria to the uroepithelium and immune dysfunction. The tendency to develop these infections could be even higher in patients with T2DM treated with SGLT-2 inhibitors, because of an increase of glucosuria (44). This phenomenon has been confirmed in both CVOTs, the EMPA-REG Outcome trial (16) and CANVAS Program (17), which will be reviewed in the next section.

Also, the FDA issued a warning of a potential risk of euglycaemic diabetic ketoacidosis, after post-marketing surveillance revealed more than 70 cases since the release of the drug class in 2015 (45). Both EMPA-REG Outcome and CANVAS Program showed no increased risk, but the low event rate could affect the results (16, 17). Diabetic ketoacidosis typically occurs in diabetes type 1 and not what one would expect in diabetes type 2. However, SGLT-2 inhibitors induce glucosuria and therefore, lower plasma glucose levels. Consequently, there is less stimulus for insulin release and this results in a decrease in circulating insulin levels. In contrast, plasma glucagon concentrations increase by two mechanisms: partly due to diminished paracrine inhibition by insulin, and also because of decreased SGLT-2 mediated glucose transport into α-cells. The decrease in circulating insulin levels leads to an increase in lipolysis in adipose tissue and ketogenesis in the liver, and thus more circulating ketones in the body (45). However, this hypothetical mechanism needs more research, and further post-marketing surveillance and future trials will clarify the potential risk. For now, caution is recommended and one might consider discontinuation of the drug during periods of acute illness and hospitalisation.

Furthermore, there are some additional adverse events reported regarding canagliflozin, which are not described with empagliflozin. There seems to be an increased risk of both lower limb amputations, predominantly toe and midfoot (HR 1.97, P<0.001), and bone fractures (HR 1.26, P=0.02) (17), corresponding with a three-year number needed to harm (NNH) of respectively 115 and 96 patients because of the low event rate. Neither bone fracture nor lower-limb amputation has been documented with the other SGLT-2 inhibitors, but additional evaluation is needed.

Finally, the FDA alerts for acute kidney injury with canagliflozin and dapagliflozin, occurring in approximately half of the cases within one month of initiation (46). In contrast, both EMPA-REG Outcome trial and CANVAS Program suggested a beneficial drug class effect regarding nephropathy, with empagliflozin even showing a statistically significant reduction in nephropathy (HR 0.61, 95% CI 0.53-0.70) (16). In determining the long-term renal effects, an analysis was made of 4124 patients within the EMPA-REG Outcome trial. Empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than placebo (47). This possible renal protection is likely multifactorial, and could be explained by glycaemic control, reducing the risk of albuminuria, and a reduction in intraglomerular pressure by preventing hyperfiltration. Nevertheless, only patients with a glomerular filtration rate (GFR) above 30ml/min/1.73m^2 were included in both trials, meaning it should not be used when this condition is not fulfilled (16, 17). Furthermore, a dose reduction is appropriate when there is a moderate renal impairment (GFR 30-60ml/min/1.73m^2). This renal outcome will be further investigated in the future trials.

3.4.2. Cardiovascular outcome

There are a growing number of trials assessing clinically important CV health outcomes in patients taking SGLT-2 inhibitors. To date, there are 2 CVOTs completed : the EMPA-REG Outcome trial and the CANVAS Program.

In the EMPA-REG Outcome trial (16), 7020 patients with T2DM at high CV risk received either empagliflozin (10 or 25mg) or placebo in addition to standard care. After a median follow-up of 3.1 years, empagliflozin was found to reduce the primary composite outcome of CV death, non-fatal MI and stroke by 14% (P=0.04 for superiority), which was based on a significant reduction in CV mortality (3.7% vs. 5.9% favouring empagliflozin; HR 0.62, 95% CI 0.49-0.77). There were numerical, but not statistically significant differences in nonfatal MI (4.5% vs. 5.2% favouring empagliflozin) and nonfatal stroke (3.2% vs. 2.6% favouring placebo). Findings were similar in the individual empagliflozin dose groups (16). Remarkable is the speed of the divergence of the survival curves: within 3 months of initiation of treatment, more patients in the placebo group died from CV disease. This was completely unprecedented, since in other CVOTs, it takes at least 1 year before the effect of intervention becomes apparent (48).

The CANVAS Program was originally designed in 2 phases to establish the CV protective effects of canagliflozin in high-risk patients with T2DM. The study included patients with either a symptomatic presentation of CV disease, or those having multiple CV risk factors. The first phase was included in the meta-analysis presented to the FDA for regulatory approval, which ruled out an HR upper limit of 1.8. However, these results were publicly disclosed at an advisory committee meeting in 2013 after partial unblinding due to an observed dose-dependent increase in LDL-cholesterol. The CV event data were also disclosed, which had the potential to compromise the post-marketing phase of the trial to fulfil the requirement of ruling out an HR upper limit of 1.3. However, the FDA accepted an integrated analysis plan, whereby data from extended follow-up of the CANVAS first phase, before and after the data disclosure, would be combined with new data from CANVAS-R to address CV safety. Data from CANVAS after the data disclosure in combination with CANVAS-R was prespecified as the principal data set for analysis for superiority of all-cause mortality and CV death (49). Finally, a total of 10,142 patients were included in the CANVAS Program, and after a median follow-up of 2.4 years, the rate of the primary outcome (i.e. a composite of CV death, nonfatal MI or stroke) was lower with canagliflozin than with placebo (HR 0.86, P=0.02 for superiority), although the reductions in the occurrence of the individual components were not statistically significant, and unlike empagliflozin, there was no evident benefit for CV or all-cause mortality with canagliflozin (17). It is however, debatable, from a rigorous statistical perspective, whether an inference of superiority is justified because it was apparently not prespecified in the testing sequence (49).

Furthermore, recent CVOTs have focused attention on the pressing problem of HF, which affects older people with diabetes more frequently than MI. Empagliflozin caused an early reduction in hospitalization or death due to HF (HR 0.61, P<0.001) (16). Canagliflozin also had favourable effects on HF, although not statistically significant (17). This was, however, achieved on top of standard of care therapy, including RAS-inhibitors, diuretics and beta blockers. Although EMPA-REG Outcome trial was not designed to assess the outcome of HF, the findings suggest an aspect of interest (50).

Overall, the results of EMPA-REG Outcome and CANVAS Program suggest a possible drug class benefit regarding a 3-point MACE in patients with T2DM and established CV disease. The FDA even approved empagliflozin to reduce the risk of CV death in adult patients with T2DM and CV disease,

even with CV death being a secondary outcome. The American Diabetes Association endorsed this recommendation in its *Standards of Medical Care in Diabetes* (49). Moreover, the *European Society of Cardiology guidelines* recommends the use of empagliflozin in patients with T2DM for preventing or delaying the onset of HF, or prolonging life (18).

However, there are some concerns about these trials, since discontinuation of a study drug (25.4% in EMPA-REG Outcome and 29% in CANVAS) and greater use of other glucose-lowering and antihypertensive agents in the placebo group, may have resulted in under- or overestimation of any benefits and risks associated with these SGLT-2 inhibitors (16, 17). The proportion of patients who had adverse events leading to discontinuation were similar though, in both drug as placebo groups (16, 17). Moreover, nearly 40% of CV deaths in EMPA-REG Outcome were non-assessable deaths that were presumed to be cardiovascular because of lack of information. When these deaths of uncertain cause were removed from the primary event analysis, empagliflozin lost all superiority over placebo (HR 0.90, 95% CI 0.77-1.06) (51). Also, there is a gradual drop over time in number of patients in the EMPA-REG Outcome trial, even though this was partly due to the study design; at 48 months, less than 10% of the initial cohort were in active research, and, especially given the unusual bend in the Kaplan Meier curve, one might question the validity of quantitative conclusions on CV outcome risk reduction. Even more, there was no prespecified time of follow-up.

The mechanism of action is probably multidimensional. Regarding CV risk factors, patients taking empa- and canagliflozin had lower HbA1c levels, but only non-significant reductions in weight, systolic and diastolic blood pressure (17), which is not enough to explain the outcome. Benefits were seen within 3 months of study enrolment with empagliflozin, and attempts made to rationalise the outcome has led to different hypotheses, such as the possibility of a "diuretic effect". Since the outcome was uninfluenced by renal function, nor by the presence or absence of heart failure, it is possible that there is more to it. In contrast, the CV benefit in the CANVAS Program was not seen until after 12 months, favouring hypotheses like endothelial changes and heart remodelling; a CV risk reduction based on reduced atherosclerosis is too early in our opinion. The difference in outcome compared to EMPA-REG Outcome trial could be explained by the inclusion of both high- and low-CV risk patients (17), but could also be related to the difference in their relative selectivity for SGLT-2 receptors: empagliflozin is more selective for SGLT-2 than canagliflozin, which could suggest an association of CV outcome to receptor selectivity.

Nevertheless, more research is needed to elucidate the underlying mechanisms, confirm whether the CV benefits are a class effect, and determine whether empagliflozin conveys a CV benefit to patients without established CV disease or T2DM (49). The CVOTs to date have been carried out in high-risk populations to increase the hazard rate of major CV events and complete the studies in a relatively brief period of time. Future studies are likely to give more conclusive results whether these SGLT-2 inhibitors will have similar effects in the majority of persons with T2DM who do not have overt CV disease. Ongoing trials are the DECLARE-TIMI 58 (52) and VERTIS CV Study (53), both designed for testing superiority concerning respectively dapagliflozin and ertugliflozin, a new SGLT-2 inhibitor in development, in patients with T2DM and high CV risk. Furthermore, the CREDENCE trial is examining the CV and renal effects of canagliflozin in patients with diabetic nephropathy (54).

3.5 Incretin mimetics

3.5.1. Mechanism of action

The phenomenon that oral glucose elicits a higher insulin response than intravenous glucose at identical plasma glucose profiles, is called the incretin effect (see figure 5). The incretin effect is conveyed by the 2 incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Both hormones are secreted from the small intestine in response to nutrient ingestion. They have hormonal effects on multiple organs and act through specific receptors: the GLP-1 receptor is expressed in pancreatic islet alpha and beta cells, heart, central nervous system, kidney, lung and gastrointestinal tract, while the GIP receptor is expressed predominantly in the pancreatic islet beta cells and less so in the central nervous system and adipose tissue. Their predominant role is regulation of (postprandial) glucose homeostasis. Activation of both incretin receptors on β-cells leads to rapid increases in levels of insulin, in a glucose-dependent manner. Moreover, consistent with the distribution of GLP-1 receptor expression, GLP-1 also inhibits glucagon secretion, delays gastric emptying and suppresses appetite. Because of the glucose dependency of the mechanism, the patient is protected from hypoglycaemia. Incretin hormones are rapidly degraded by dipeptidyl peptidase-4 (DPP-4) (see figure 5) (55).

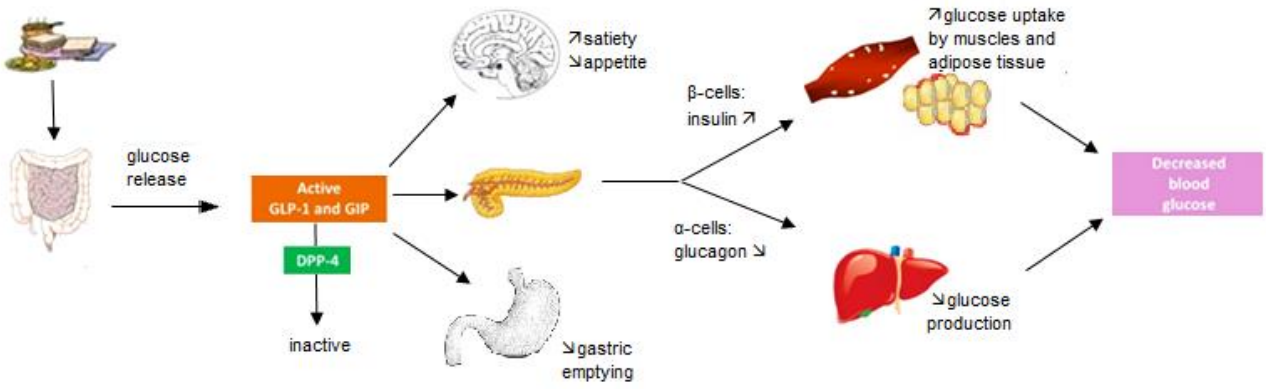


Fig. 5: Role of incretins in glucose homeostasis

Now, the incretin response is markedly attenuated in people with T2DM. While GLP-1 concentrations are reduced in individuals with T2DM, its insulinotropic action is relatively well preserved. By contrast, while GIP concentrations are largely unaffected in T2DM, its insulinotropic action is impaired (56).

Two pharmacological approaches have been taken to enhance the incretin response, which will we reviewed below.

3.5.2. GLP-1 agonists

The first approach is to administer GLP-1 receptor agonists that are resistant to cleavage by DPP-4 and provide pharmacological levels of GLP-1 activity. This will provide effective glycaemic control and weight reduction, since it promotes satiety and slows gastric emptying (56). They are currently only available for parenteral administration, given once weekly or once or twice daily, and either long-acting (dulaglutide, albiglutide) or short-acting (exenatide, liraglutide, lixisenatide) drugs. Semaglutide is a long-acting GLP-1 agonist and was recently approved by the FDA to be administered as a once-weekly injection, while the daily oral version is still in development.

Because of the delayed gastric emptying, it is not surprising that all of the GLP-1 agonists can cause adverse gastro-intestinal symptoms, such as nausea and vomiting, especially on initiation. The once weekly agents seem to be better tolerated than the daily options (57), and these symptoms can be reduced by gradual dose titration as well (1). These gastro-intestinal adverse effects were a principal reason for the greater portion of premature discontinuation with liraglutide and semaglutide in respectively the LEADER and SUSTAIN-6 trial, two of the CVOTs that will be reviewed in the next section (15, 58).

Next, there is the possibility of a local skin reaction on the injection site, which is more common in weekly administration compared to the daily injections (59).

Also, caution is warranted in case of decreased kidney function, and screening is advised upon initiation. In the ELIXA and EXSCEL trial, 2 other CVOTs discussed later, patients with an eGFR<30ml/min/1.73m^2 were excluded, while in the LEADER and SUSTAIN-6 trial, this only applied to patients getting continuous renal replacement therapy. In contrast, the latter two trials showed a reduction in nephropathy events (HR 0.78, P=0.003 and HR 0.64, P=0.005 respectively), and a neutral effect in ELIXA and EXSCEL trial (15, 58, 60, 61). The exclusion criteria feel thus discrepant compared to the outcome, and more research should be done concerning this (possible beneficial) renal effect. Rates of retinopathy complications, however, were significantly higher with semaglutide (HR 1.76, P=0.02), but were not seen with the other study drugs (58).

Furthermore, studies in animals have suggested a higher incidence of thyroid C-cell adenomas and carcinomas with GLP-1 agonists, but this finding has not been replicated in humans for now (61). In all trials, the rates of pancreatitis and neoplasms differed not significantly from placebo (58, 60, 61), although the LEADER and EXSCEL trial have numerically higher cancer rates (15, 61). Nevertheless, these trials are not powered to determine the effect on cancer risk and can therefore neither confirm nor exclude such a possibility. With longer periods of follow-up, one should have more clarity about these long-term adverse events.

3.5.2.1 Cardiovascular outcome

The CV safety of GLP-1 receptor agonists has been assessed in 8 trials, of which 4 have reported outcomes. A fifth trial, the FREEDOM-CVO trial, which evaluated continuous delivery of exenatide, has been completed, but not reported yet (62). Regarding albiglutide, dulaglutide and semaglutide, CVOTs are scheduled for completion within the next 1-2 years with respectively the HARMONY (63), REWIND (64) and PIONEER-6 trial (65).

The ELIXA trial (60) is a RCT conducted in 6068 patients with T2DM who had a recent coronary event. The patients received either daily injections with lixisenatide or placebo, in addition to standard care,

and were followed for a median of 2.08 years. The primary end point, a composite of a 4-point MACE, including CV death, MI, stroke and hospitalisation for unstable angina, showed non-inferiority compared to placebo (HR 1.02, P<0.001), but no superiority (60).

The EXSCEL trial (61) had a similar outcome, comparing weekly exenatide with placebo. There is currently no CVOT available for daily injections with exenatide. Exenatide showed safety (HR 0.91, P<0,001), but no superiority (P=0.06), although it included more patients (i.e. 14,752 patients) and had a longer time of follow-up (3.2 years). In contrast to ELIXA however, the EXSCEL trial included also diabetic patients without previous CV events, counting for 27% of the study population (61). Of interest, the treatment persistence was low, with 43% drug discontinuation, probably because of the pragmatic nature of the study design, with visits every 6 months and limited study support. Nevertheless is it remarkable that, despite this limited drug exposure and a heterogeneous population of whom 27% had no history of CVD, the 3-point MACE reduction of 9% came so close to reaching statistical significance (49).

Consistent with these results is the SUSTAIN-6 trial (58) regarding once-weekly treatment with semaglutide, although on smaller scale. A total of 3297 T2DM patients were included, having established CV disease, chronic HF (NYHA class II or III), chronic kidney disease of stage 3 or higher, or an age of 60 years or more with at least one CV risk factor. After a median follow-up of 2.1 years, the primary composite outcome of a 3-point MACE showed non-inferiority (HR 0.74, P<0.001), but superiority analysis was not prespecified (58).

In contrast, the LEADER trial (15) was powered to show superiority and achieved expectations. This was a RCT of 9340 patients with T2DM at high risk for a CV event, followed for a median time of 3.8 years. The primary outcome of a 3-point MACE showed a risk reduction of 13% (P=0.01) in favour of once-daily liraglutide compared to placebo, but analysing the individual components, there was only a statistically significant reduction regarding CV death (HR 0.78, P=0.007) with numerical, but not statistically significant, differences in nonfatal MI and stroke favouring liraglutide. Moreover, the results were very similar in patient with or without previous MI or stroke. In case of CV death, time to benefit was 12 months (15). Liraglutide already had the indication for weight reduction in obese patients after data from the SCALE Obesity and Pre-diabetes trial (66). As a result of the LEADER trial, the FDA approved an additional indication for liraglutide: to reduce the risk of MACE in adults with T2DM and established CV disease.

The difference in CV outcome of these GLP-1 agonists is probably multidimensional. When analysing cardiometabolic risk factors, the impact of treatment differed in terms of glycaemic control[1] and weight reduction[2], with similar, but limited lowering of systolic blood pressure and LDL-cholesterol. To date, head-to-head comparisons of GLP-1 agonists have suggested a modest advantage in HbA1c and weight reduction for liraglutide (57). However, usual care-regimes were not standardized in all trials, and disproportionate use in placebo groups of additional CV medications (including antihypertensive agents, diuretics, and lipid-lowering medications) and diabetes therapies, known to reduce CV risk, could underestimate the CV outcome of all GLP-1 agonists. The heterogeneity in

[1] glycaemic difference compared to placebo (P<0.001): ELIXA -0.27%, EXSCEL -0.53%, SUSTAIN-6 up to 1%, LEADER -0.4%

[2] weight difference compared to placebo (P<0.001): ELIXA -0.7kg, EXSCEL -1.27kg, SUSTAIN-6 up to -4.3kg, LEADER -2.3kg

outcome might reflect differences in pharmacokinetic and pharmacodynamic properties as well (e.g. short- versus long-acting drugs, structural similarity to human GLP-1, ...), but it could be mainly the result of differences in study populations, trial designs, and treatment persistence. For instance, the time of follow-up differed significantly, with the LEADER trial having the longest period of follow-up. The duration of the trials was apparently enough to observe sufficient numbers of CV events so that they could reasonably exclude a major benefit, as well as unanticipated harm, but there would be less ambiguity when we could compare trials with an equal and longer time of follow-up.

3.5.3. DPP-4 inhibitors

The other approach is to inhibit dipeptidyl peptidase-4 (DPP-4) activity through DPP-4 inhibitors, which increases the half-life of the incretin hormones, and restore physiological levels of GLP-1 and GIP. They also improve glycaemic control, but are weight-neutral, in contrast to the weight reduction with GLP-1 agonists (56). There are 5 different DPP-4 inhibitors available for adjuvant therapy in T2DM treatment : alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin. They are taken orally once or twice per day.

Overall, the DPP-4 inhibitors seem to be well-tolerated (67-69). The hypoglycaemia risk is low, with the exception of saxagliptin, but could rise in combination with SU (59). They seem safe in patients with impaired renal function as well. However, a dose reduction is necessary in patients with moderate to severe renal impairment (1), except for linagliptin, which is metabolised in the liver (59). After all, patients with an eGFR<30 ml/min/1.73m^2 were not included in the TECOS trial (69), and patients with end-stage renal disease were excluded from the SAVOR and EXAMINE trial (67, 68), which will all be reviewed in the next section.

There were some observational reports of a potential association with pancreatitis and pancreatic cancer (67), although the safety end points in all CVOTs did not support this (67-69).

3.5.3.1 Cardiovascular outcome

To date, there are only CVOTs available for alogliptin, saxagliptin and sitagliptin. A CVOT with linagliptin is still running as the CARMELINA trial, evaluating the CV outcome of patients with T2DM, CV risk and evidence of impaired kidney function (70), and the CAROLINA trial is comparing linagliptin to glimepiride (71). For now, there are no future trials planned with vildagliptin.

In the SAVOR-TIMI 53 trial (67) 16,492 patients with T2DM and a history of a CV event or multiple CV risk factors, were randomly assigned to either saxagliptin or placebo. After a median follow-up of 2.1 years, the primary composite endpoint of the usual 3-point MACE showed non-inferiority with a HR of 1.00 (P<0.001), but no superiority. The secondary endpoint showed no cardioprotective benefit either. Moreover, when looking at the individual components, there seem to be a higher rate of patients in the saxagliptin group who had to be hospitalised for HF (HR 1.27, P<0.007), but without increased risk of fatal outcome (67).

Very similar results were seen with alogliptin in the EXAMINE trial (68). This RCT allocated 5380 patients with T2DM, who had a recent acute coronary syndrome, to alogliptin or placebo. The primary end point of the same 3-point MACE showed non-inferiority as well (HR 0.96, P<0.001). Since the findings indicated no superiority, the study was stopped prematurely after a median duration of 1.46 years. As with saxagliptin, the same concern about heart failure was raised, with a HR of 1.19,

although not statistically significant. Despite this, there was no increased risk in the composite of hospitalisation for HF or CV death in a post-hoc analysis (68).

Finally, the TECOS trial is a RCT of 14,671 patients with T2DM and established CV disease, receiving either sitagliptin or placebo. The study continued for a median of 3.0 years, until the requisite minimum of patients had a primary outcome event, which consisted of a 3-point MACE or hospitalisation for unstable angina. Sitagliptin was non-inferior to placebo with a hazard ratio of 0.98 ($P<0.001$), but showed no superiority, consistent with the other DPP-4 inhibitors mentioned above. There was, however, no increased risk of hospital admission due to heart failure (HR 1.00, $P=0.98$) (69).

In conclusion, none of these DPP-4 inhibitors were associated with any suggestion of CV benefit, but they are safe compared to placebo in terms of major adverse cardiovascular events. However, the FDA added a warning to saxagliptin and alagliptin concerning the risk of heart failure. The reasons for the lack of a heart-failure safety signal may relate to differences in the patients who were enrolled, in the background care that was provided, in the recording and definition of HF events or in pharmacologic differences among DPP-4 inhibitors. More research has to be done, but for now, we have to take this into account and avoid their use in patients with pre-existing heart failure or kidney disease.

The impact of treatment on cardiometabolic risk factors with DPP-4 inhibitors was minimal, except for small reductions in HbA1c at study end. It is unclear whether the difference in HbA1c lowering of -0.3% compared to placebo (67-69), effects CV outcome in such a short follow-up time. However, with the pursuit of glycaemic equipoise by increasing antidiabetic medication where applicable, disproportionate use of diabetes therapies known to reduce CV risk may have resulted in lower event rates in the placebo group, and therefore confounding the results, as seen with the GLP-1 agonists.

However, by neutralising these risk factors, the effect of the drug on CV events can be evaluated "independently". It is merely a play of pharmacokinetic and pharmacodynamic properties of the studied drug, and differences in study populations and trial design. Both the SAVOR and TECOS trial included a very large population, but all trials, the EXAMINE trial in particular, were relatively short in duration. Longer-term treatment could possibly provide both benefits and adverse events which cannot be detected on short term. The same applies to a different study population, where patients with more complicated co-existing illnesses can clarify other potential adverse events.

4. Discussion

The increased CV risk with T2DM is well recognised, and atherosclerotic heart disease, stroke, peripheral vascular disease, and heart failure account in large part for the excess death rate. Therefore, it is of the greatest importance that antidiabetic medication is safe in terms of CV outcome, or even shows a clinically relevant CV benefit. This has been assessed in the CVOTs we reported earlier, and are now discussed in terms of reliability.

Metformin trials show a reduction in all-cause mortality rate, but lack a clear statistical benefit in terms of macrovascular outcome, as assessed in the UKDPS. However, the UKPDS included a CV low-risk population and the standard of care for CV risk factors in 1977 were different from the ones we use today. SUs seem safe, but there are only a few trials assessing this issue, and not all powered to address CV outcome. Considering that metformin is the first-line treatment for T2DM and SU is also a very common therapeutic tool in diabetes, CVOTs on these drugs, following the current FDA guidelines, should be essential to provide clarity, more so because they are used as standard care, add-on therapy or active comparator in current CVOTs. However, since the patent for metformin expired in 2003 and will be for SU in only a few years, no drug company has been interested in funding studies that include these antihyperglycaemic drugs, so it has become a task of universities.

However, for the majority of other antidiabetic drug classes, there are several CVOTs available. Thiazolidinediones, for example, have also been available for almost decades. The original enthusiasm of the late 1990s/early 2000s was comparable to that of the SGLT-2 inhibitors today. However, this was overshadowed by the CV concerns surrounding rosiglitazone, even though these were never corroborated and even countered by prospective data and the results of the PROactive trial. Nevertheless, the PROactive trial is often described as a non-inferiority trial, although the secondary outcome demonstrate a clear reduction in a 3-point MACE, completely comparable to the highly acclaimed results from the LEADER and EMPA-REG Outcome trial. Even though a secondary outcome is considered to be less statistically "robust", we would like to point out that the secondary outcome of the PROactive trial is used as the preferred primary composite outcome in current CVOTs, with the exception of all-cause mortality instead of CV mortality as one of the components of the 3-point MACE. Although the CV deaths were assessed individually and were similar in both study groups, all fatal events were classified as CV, unless there was a clear non-cardiovascular cause. This could compromise the results if not all-cause mortality was used as a component instead of CV mortality, unlike the EMPA-REG Outcome trial (see below). Moreover, CV mortality is a secondary outcome in the EMPA-REG Outcome and LEADER trial, and considered an important outcome nonetheless. Especially considering the large sample size of the PROactive trial, the secondary outcome is not an outcome to ignore.

The IRIS trial even shows a reduction in MI and stroke with pioglitazone in insulin resistant non-diabetic patients who had a recent stroke or TIA. This supports the outcome of the PROactive trial and suggests that the increase in insulin sensitivity through pioglitazone is an important factor in reducing macrovascular complications.

Although it is regrettable that the PROactive trial was terminated prematurely, because of the higher CV event and thus enrolment rate, one may wonder whether a longer time of follow-up could have change the results. After all, time-to-event analyses are the format of current CVOTs, so we do not expect a different outcome in case of a longer trial duration.

Despite these results, the chance of heart failure (HF) in patients who are at risk result in the reservation of prescribing pioglitazone. It is not clear to what extent however, since patients with a

history of NYHA Class 3 and 4 HF were excluded in trials and because there are no diagnostic criteria in study protocols, leading sometimes to edema of lower limbs to be reported as HF, whereas edema is a known side effect of thiazolidinediones, regardless of HF. Nevertheless, based on current data, we would recommend caution in their use in patients with a history of HF, and perhaps to refrain from using them, until they are proven safe.

A similar concern about HF is raised with DPP-4 inhibitors, although the results are inconclusive. In contrast, SGLT-2 inhibitors seem to reduce hospitalisation for HF on top of standard of care. Although these trials were not designed to assess the outcome of HF, the findings suggest an aspect of interest and require confirmation in future trials. A combination of pioglitazone and empagliflozin has therefore been suggested as a particular beneficial combination. This however, has not been investigated yet.

In conclusion, the results of the PROactive, IRIS and TOSCA.IT trial indicate that pioglitazone reduces CV morbidity and mortality in insulin resistant and diabetic patients with CV high-risk, and could be an important and cheap asset to our arsenal of antidiabetic drugs, next to empagliflozin, canagliflozin and liraglutide, provided that patients with heart failure are exempted from its use.

Regarding the CVOTs published after the FDA regulation, each trial demonstrated non-inferiority to placebo in their primary end point, while three of them provided evidence of significant decreases: liraglutide, empagliflozin and canagliflozin. However, the individual components of the 3-point MACE did not reach statistical significance, except for CV mortality in EMPA-REG Outcome and LEADER trial. Also, the partial unblinding of results in the first phase of the CANVAS Program could influence the outcome, but the FDA accepted to combine data from CANVAS after the data disclosure in combination with data in CANVAS-R to address superiority. This would underline the reason why it would seem odd to dismiss the PROactive results as statistically unsound for the same reasons: it would be somewhat strange to reject the one while being admissive of the other. The explanation for the CV benefit in these three drugs is probably multidimensional, with a reduction in some of the CV risk factors, as well as differences in pharmacokinetic and pharmacodynamic properties and differences in study population and trial design.

As mentioned earlier, with the results of the EMPA-REG Outcome and LEADER trial, the FDA approved both empagliflozin and liraglutide for reducing the risk of MI, stroke and CV death in patients with T2DM who have established CV disease. The European Society of Cardiology even recommends the use of empagliflozin for prolonging life in high-CV risk patients with T2DM, as well as for preventing or delaying heart failure (18).

One may however, question this conclusion. Thiazolidinediones had a similar course after all, with a very promising beginning, and later on maligned for side effects. Likewise, we do not know anything about long-term effects of SGLT-2 inhibitors, because of the short duration of trials. The FDA recently issued warnings about ketoacidosis for SGLT-2 inhibitors, especially with canagiflozin, to a lesser extent with dapagliflozin and rarely with empagliflozin. This could relate again to their receptor selectivity, but this finding was only reported during post-marketing surveillance and not seen in current CVOTs.

Also, there are only hypotheses about the mechanism of CV reduction with empagliflozin. Is it truly related to a diuretic effect, or are there other mechanisms involved? Since the outcome was uninfluenced by renal function, nor by the presence or absence of heart failure, there is probably more to it than a mere diuretic effect. A head-to-head comparison of empagliflozin and a diuretic could deliver us more insight in the process.

Next, the drug discontinuation in the CVOTs of SGLT-2 inhibitors is remarkable: more than 25% of patients discontinued both EMPA-REG Outcome and CANVAS trial prematurely, which could again under- or overestimate both benefits and risks. In comparison, a similar drug discontinuation was seen in the IRIS trial, which is less surprising since it was used as an add-on to standard therapy and was therefore given as an extra to non-diabetic patients. In PROactive, discontinuation was 16%.

Finally, there are some aspects about the EMPA-REG Outcome trial in particular that puts empagliflozin into perspective. The difference in CV deaths between the 2 study groups was the main factor responsible for the observed difference in the 3-point MACE. However, nearly 40% of the CV deaths reported in the trial were not unequivocally CV in origin and, when these deaths were removed from the primary event analysis, empagliflozin lost all superiority over placebo (51). Second, the drug had no statistically significant effect on stroke or MI, with even numerically more strokes. Preferably, both CV death and complications move in the same direction, especially with the advantage of better glycaemic control and lower blood pressure (48), although not one CVOT has yet shown a reduction in all components of the 3-point MACE. Third, we would like to point out that, at 48 months, less than 10% of the cohort remained to be evaluated. Although a gradual drop over time is to be expected in time-driven studies, we question the quantitative label given to the CV risk reduction. Last but not least, there was no prespecified minimum time of follow-up, in contrast to LEADER trial, which could compromise the results again.

General limitations of current CVOTs : how to put CVOTs into perspective ?

Questions remain whether the information obtained through these CVOTs, designed according to the FDA mandate, justifies the time and resources needed, especially in light of the neutral CV results of many of these studies (49). Setting things straight, there are some general limitations in current CVOTs that we will point out, some of them already reviewed earlier.

First, there is a **lack of generalisability** of findings to the entire population of patients with T2DM. To answer questions of safety and efficacy, trials are event-driven to provide an adequate number of events in an acceptable period of time. Therefore, the patients included usually have a CV high-risk. These patients cannot be representative of the general population, and the results are so far only valid for the particular patient groups enrolled in the studies. It is not clear yet how translatable they are to patients with a shorter duration of diabetes or without established CV complications. To achieve a statistically significant number of MACE events, this will require larger and/or longer studies but would yield valuable information about CVD prevention (49). Moreover, casting a wider net of inclusion criteria to include elderly individuals, patients with various stages of chronic kidney disease and hepatic dysfunction would help identify more potential adverse outcomes (72).

Along the same lines, the **patient selection criteria** in these trials differ somewhat, which makes them hard to compare. The duration of diabetes, the established CV disease or risk factors (72) and age requirements were similar, but not identical (21). More recent CVOTs include patients with CV high-risk, which by definition lead to higher CV event rates and ensure sufficient events in a timely manner. With a lower risk population, the results show a smaller impact on CV outcome, as observed in the RECORD, UKPDS, TOSCA.IT and CANVAS trial.

The current CVOTs have also a relative **short time of follow-up**. Therefore, they can only address short-term outcomes. Given the fact that macrovascular complications in T2DM are by definition long-term issues, it is surprising to see these trials have enough power to evaluate their safety and superiority compared to placebo. The UKPDS and DCCT/EDIC trials have shown only a CV benefit long after the change in HbA1c difference disappeared, leading to the concept of a "legacy effect", possibly based on a reduction of glucose-related changes of vascular tissue structure persisting after

antidiabetic therapy, slowing the early progression of atherosclerosis. Whether any non-glycaemic effects of treatment contributed to this CV benefit cannot be determined. These observations are strong arguments in favour of an early optimisation of blood glucose control in patients with T2DM, but the short time of follow-up in current CVOTs make it impossible to confirm this. This also puts the results of short-term CV advantages into perspective and underlines the necessity of long-term follow-up. Also, in these CVOTs we have limited information about long-term non-vascular safety outcomes. Regarding the SGLT-2 inhibitors for example, only time will learn the relevance of the risk of diabetic ketoacidosis, as with cancer risk in GLP-1 agonists and DPP-4 inhibitors. In conclusion, longer-term follow-up is needed to identify any safety issues and beneficial effects that are either slowly evolving or resulting from a "legacy effect" of earlier treatment.

Third, nearly all CVOTs to date are **placebo-controlled** trials, which are perfect for determining the safety of a drug. Head-to-head comparisons are not an alternative, but could be a useful complement if the studied drug is compared to a golden standard. However, using an active comparator as control will require sufficient knowledge of the CV impact of the comparator to avoid confounding interpretation of the results (49). This may become feasible as our understanding of the CV safety of newer antidiabetic drugs increases. Combinations of antidiabetic drugs known to be cardioprotective may also need to be tested to explore whether the CV benefits are compounded (49). Examples of head-to-head comparisons are the TOSCA.IT trial, comparing pioglitazone versus SU, and the ongoing CAROLINA trial, comparing the DPP-4 inhibitor linagliptin versus the SU glimepiride.

The next limitation is the fact that there are **no standardised definitions of important outcomes** in CVOTs conducted to date. The FDA encouraged the composite of a 3-point MACE, although the TECOS and ELIXA trial have used a 4-point MACE. However, the components differ greatly in their pathophysiology : while MI has a thrombotic origin, CV death results mostly from arrhythmia and stroke can either be a product of thrombotic origin or haemorrhage. These differences should be taken into account when designing and analysing composite end-points, because a positive or neutral effect in one of the components does not necessarily mean an improvement in the others, as exemplified by the results in EMPA-REG OUTCOME (21). However, using composite outcomes increases the statistical efficiency because of higher event rates, and reduces sample size, costs and time, therefore making it an interesting primary outcome (72). Future CVOTs should standardise the definitions of important outcomes, including safety and microvascular outcomes. If there is adequate power, it may be more desirable to evaluate key efficacy and safety outcomes separately as predefined co-primary endpoints, with superiority and non-inferiority analyses respectively (49). In a very similar vein, important secondary outcomes, like mortality or serious morbidity events, should not be dismissed if the primary composite outcome is not achieved, as in the PROactive trial; they should be independently considered.

Fifth, trials are performed on a **standard of care** background. One tries to achieve glycaemic equipoise in both study drug population and placebo, as well as encourage near-optimal CV risk management through the use of statins, antiplatelet and antihypertensive medication. Neutralising the effect of glycaemia, cholesterol and blood pressure, leaves only the "unknown" factors to play out in deciding the CV effects of the studied drug. However, since usual-care regimes were not standardised in all trials, disproportionate use in the placebo group of antihypertensive, lipid-lowering and diabetes therapies with possibly a beneficial or adverse effect on CV events, may have influenced event rates in the placebo groups, thereby under- or overestimating both benefits and risks.

5. Conclusion

The CVOTs to date are providing evidence of CV safety of the available antidiabetic drugs. In addition, it seems that there are a few drugs of interest when it comes to actual lowering the CV risk in CV high-risk type 2 diabetes: pioglitazone, liraglutide, empagliflozin and canagliflozin have shown promising results in their CVOTs. Nevertheless, the trials were performed in the light of secondary prevention of cardiovascular disease, and it is important to realise the outcomes are not applicable to the general diabetic population. Future trials might benefit from focusing on diabetic patients with a lower CV risk.

Furthermore, there are some limitations as well in these trials, which we should bear in mind when interpreting the outcomes. Apart from their lack of generalisability, the trials have a relative short time of follow-up, inconsistency throughout the outcomes and standard of care, and sometimes questionable statistical analysis. In this light, the alleged superiority of empagliflozin is questionable and we would recommend keeping the above-mentioned limitations into account when choosing anti-diabetic drugs, even in the context of current treatment guidelines. We would encourage tailoring the choice of medication to the patient, including possible pleiotropic drug effects, as well as costs, given the high and ever increasing prevalence of type 2 diabetes mellitus.

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