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Editorial

Invited review. Series: Implications of the recent CVOTs in type 2 diabetes
Which patients for GLP-1RA or SGLT-2 inhibitor?

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ABSTRACT

Large cardiovascular outcome trials (CVOTs) have lent support to a cardiovascular protection with the use of SGLT2-inhibitors (SGLT2is) and GLP1-Receptor Agonists (GLP1-RAs) in subjects with type 2 diabetes. These two classes of novel glucose lowering agents have been shown to have a similar effect on the risk reduction of Major Adverse Cardiovascular Events (MACE: nonfatal myocardial infarction, nonfatal stroke, cardiovascular mortality). Nonetheless, they may not be simply interchangeable. Rather, careful evaluation of all the results of CVOTs leads identification of different effects that may allow profiling of the ideal individuals with T2DM who may benefit most from the use of one or the other class of agents. These differences include effect on heart failure, stroke and diabetic kidney disease that have prompt recent guidelines and recommendation for the treatment of type 2 diabetes to suggest the preferential use of SGLT2is in those with evidence of heart failure and impaired kidney function, while both SGLT2i and GLP1-RAs with proven effect could be use in those with prevalent atherosclerotic cardiovascular disease. This review discusses all these elements of differentiation along with others that in the future may help establishing the best cardiorenal benefit for individuals with T2DM.

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1. Introduction

Since the turn of the century the curve of cardiovascular (CV) morbidity and mortality among people with type 2 diabetes (T2DM) has been significantly and continuously declining. Thus, the standardized incidence rate of hospitalization for CV disease has dropped from 380 events per 10,000 patient-yr in 1998-99 to about 180 events per 10,000 patient-yr in 2012–13 [1]. Similarly, CV death went from 180 to 90 deaths per 10,000 patient-yr. This 50% reduction in just 15 years represents a major achievement, which is most likely accounted for by more effective CV risk reduction as well as by more efficacious rescue treatments at the time of an acute CV event. Though this may be seen as a success of modern medicine, we are still far from having abolished the excess of CV risk that characterizes T2DM [1]. In 2015 the Emerging Risk Factor

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Collaboration showed how subjects with T2DM still had twice as much the risk for CV death as compared to individuals without T2DM even when they are matched for baseline CV risk [2].

In order to fill this gap novel therapeutic strategies should be developed. Whether tight glycemic control could contribute to this purpose it has been the matter of high-spirited trials [3–6]. These studies, however, have been largely inconclusive to generate a sense of frustration among diabetologists [7]. In fact, they show only a minor effect mostly limited to a 18% risk reduction for myocardial infarction [8]. Not only the effect of glycemic control has been difficult to ascertain but it was also suggested that intensive treatment should be implemented with caution because of unwanted risk of severe hypoglycemia and potentially fatal consequences, leading to the concept of target and treatment individualization [9]. To make this scenario even more complex was the claim that some glucose-lowering agents could actually increase CV risk [10]. As a result of all this, the Food and Drug Administration (FDA) requested that all new glucose-lowering agents have to be tested for CV safety. This request has resulted in an unprecedented series of CV Outcomes Trials (CVOTs).

The first drugs to be tested were the DPP-4 inhibitors (DPP4is) saxagliptin [11] and aloglitptin [12] showing no increased risk of 3-point Major Adverse Cardiovascular Events (MACE: nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death), though some concern was raised because of an unexpected increase in hospitalization for heart failure (hHF). Such a risk was not confirmed in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), which also was neutral with respect to MACE [13]. These findings have been recently corroborated by the results of the CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin (CARMELINA) [14] and the CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes (CAROLINA) [15] where the safety of linagliptin was evaluated in T2DM populations enriched with impaired kidney function and CV risk, respectively.

After the first 3 CVOTs with DPP-4is the results of the first trial with a GLP1-receptor agonist (GLP1-RA) was published. The Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes After Acute Coronary Syndrome During Treatment with Lixisenatide (ELIXA) [16] showed neutrality with respect of CV events with the use of lixisenatide in patients with acute coronary syndrome within 90 days before entering the study.

Though these studies met the safety criteria set up by the FDA, they did suggest any specific advantage in term of CV protection, generating perplexities within the diabetes community with respect to the need for enormous efforts and monetary investments [17]. It really was in the midst of this skeptical atmosphere that the results of the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME) EMPA-REG trial were published.

2. A new series of positive CVOTs

The EMPA-REG was a randomized, double blind, placebo-controlled trial assessing CV safety of empagliflozin (EMPA) in T2DM patients with prior history of CV events [18] (Table 1). Patients were randomized to EMPA 10 mg and 25 mg or placebo and followed for just over 3 years. The primary composite outcome, the classic 3-point MACE, occurred in fewer patients on EMPA with a hazard ratio (HR) of 0.86 (95% CI, 0.74–0.99; $p = 0.04$ for superiority). This was accompanied by a reduction of the risk for death from CV causes (HR 0.62; 95% CI, 0.49–0.77; $p < 0.001$), death from any cause (HR, 0.68; 95% CI, 0.57–0.82, $p < 0.001$), and hHF (HR 0.65; 95% CI, 0.50–0.85; $p = 0.002$). In summary, the EMPA-REG trial, for the first time, provided evidence for CV protection with the use of a glucose-lowering agent representing a main turning point in the treatment of T2DM. It really was a turning point also because after this trial, other studies provided positive results in a stringent sequence (Tables 1 and 2).

In the CANagliflozin cardioVascular Assessment Study (CANVAS) participants were randomly assigned to canagliflozin (CANA) or placebo (Table 1). Over a 3.6-year follow-up a risk reduction in MACE was reported (HR 0.86; 95% CI, 0.75–0.97; $p = 0.02$ for superiority) [19]. Of interest, this was obtained in a population that included 30% of subjects with no prior CV events. This proportion was even greater (66%) in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE) trial [20] that showed a numerical though non-significant risk reduction for MACE (HR, 0.93; 95% CI, 0.84–1.03; $p = 0.17$).

Along with SGLT2-inhibitors (SGLT2is), CVOTs performed with GLP1-RAs also lent support to CV protection besides the neutral results of ELIXA (16) (Table 2). The first trial to support a beneficial CV effect was the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER trial) where T2DM patients with high CV risk were randomly assigned to liraglutide (LIRA) or placebo [21]. The study showed a risk reduction of 3-point MACE (HR 0.87; 95% CI, 0.78–0.97; $p = 0.01$ for superiority). Similar results were found in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN 6) reporting a 26% reduction of the primary 3-point MACE outcome (HR 0.74; 95% CI, 0.58–0.95; $p < 0.001$) [22].

Conversely in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial, statistical significance was not formally reached (HR 0.91; 95% CI 0.83–1.00) [23] but the CV benefit of GLP1-RAs was further supported by the results of the HARMONY OUTCOMES trial. This study randomized 9463 T2DM subjects with established atherosclerotic vascular disease to albiglutide (30–50 mg) or placebo with the former reducing the risk for MACE by 22% (HR, 0.78; 95% CI, 0.68–0.90) over a median follow-up of 1.6 years [24]. Unfortunately, albiglutide is no longer available as the manufacturing company stopped producing the drug for strategic industrial reasons. The Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial [25] assessed the effect

Table 1 – Cardiovascular outcomes in major trials with SGLT2 Inhibitors.

	EMPA-REG OUTCOME	CANVAS Program	DECLARE–TIMI 58
Drug tested	Empagliflozin vs placebo	Canagliflozin vs placebo	Dapagliflozin vs placebo
Subjects, n	7,020	10,142	17,160
Duration of follow-up	Median of 3.1 years	Mean of 188.2 weeks	Median of 4.2 years
Baseline HbA1c, %	8.1 ± 0.9	8.2 ± 0.9	8.3 ± 1.2
Cardiovascular risk, %	99% prior cardiovascular disease	66% prior cardiovascular disease	40% prior cardiovascular disease
Main cardiovascular outcomes HR (95%CI)	Primary outcome 3P-MACE 0.86 (0.74–0.99) NNT = 63 Cardiovascular death 0.62 (0.49–0.77) All-cause mortality 0.68 (0.57–0.82) HF hospitalization 0.65 (0.50–0.85) Stroke 1.18 (0.89–1.56)	Primary outcome 3P-MACE 0.86 (0.75–0.97) ~NNT of 62 All-cause mortality 0.87 (0.74–1.01) Heart failure hospitalization 0.67 (0.52–0.87) Nonfatal stroke 0.90 (0.71–1.15)	Primary outcome 3P-MACE 0.93 (0.84–1.03) Non-inferior to placebo Cardiovascular death or HF hospitalization 0.83 (0.73–0.95) Cardiovascular death 0.98 (0.82–1.17) Death from non cardiovascular cause 0.88 (0.73–1.06) HF hospitalization 0.73 (0.61–0.88) Ischaemic stroke 1.01 (0.84–1.21)
Composite renal outcome measure HR (95%CI)	0.54 (0.40–075) NNT = 77	0.60 (0.47–0.77) NNT = 125	0.53 (0.43–0.66) NNT = 77

3P- MACE: 3-point major adverse cardiovascular events; NNT: number needed to treat; HF: heart failure.

of dulaglutide on MACE when added to the existing antihyperglycemic regimen in T2DM subjects with and without a prior CV event (Table 2). Dulaglutide was associated with an overall risk reduction (HR 0.88; 95% CI, 0.79–0.99; p = 0.026) that was not different between those with and without prior CV events. The favorable effect in primary prevention has been recently acknowledged by the FDA [26]. The PIONEER 6 is the last CVOT on GLP1-RAs and it is peculiar because of the use of oral semaglutide. The study, smaller as compared to other trials, found a numerical risk reduction for MACE (HR 0.79; 95% CI, 0.57–1.11; p < 0.001 for noninferiority) [27].

In summary, both SGLT2is and GLP1-RAs on top of their glucose-lowering activity have been shown to confer CV protection. A recent meta-analysis reported that both classes of drugs reduce the risk of MACE to a similar extent (GLP1-RAs: HR 0.88; 95% CI, 0.84–0.94; p < 0.001; SGLT2is: HR 0.89; 95% CI, 0.83–0.96; p = 0.001) [28] with an effect that, as a class, seems to be more pronounced in T2DM subjects with prior CV events (HR 0.86; 95% CI, 0.80–0.93; p = 0.002). However, if the two classes are equivalent in term of CV risk reduction the question arises as whether they can be used interchangeably or whether differences exist that may guide drug's selection. With respect to this question, a detailed review of the results of the available CVOTs highlights different effects of SGLT2is and GLP1-RAs with respect to heart failure, stroke, and diabetic renal disease.

3. Heart failure

When CVOTs data are pooled a clear difference becomes apparent as far as the risk reduction for hHF is concerned. In the meta-analysis by Zelniker et al [28] SGLT2is reduced the risk of hHF by 31% (HR 0.69, 95% CI 0.61–0.79) compared to a 9% reduction with GLP1-RAs (HR 0.93; 95% CI, 0.83–1.04). An even more recent meta-analysis including all GLP1-RA CVOTs [29] indicated a significant reduction of risk of hHF (HR 0.91; 95% CI, 0.83–0.99), although the overall risk reduction (9%) was superimposable to the one previously calculated [28]. The more apparent effect of SGLT2is is retained in subjects with atherosclerotic CV disease (HR 0.76; 95% CI, 0.69–0.84) and, though to a less extent, in those with multiple CV risk factors (HR 0.84; 95% CI, 0.69–1.01) as well as in those with a known history of HF (HR 0.71; 95% CI, 0.61–0.84) and those without (HR 0.79; 95% CI, 0.71–0.88) [30]. These results have been confirmed in real world studies. The CVD-Real study [31] identified after propensity matching, 309,056 patients equally split between those newly initiated on SGLT2is and those on other glucose-lowering agents. Use of SGLT2is was associated with lower rates of hHF (HR 0.61; 95% CI, 0.51–0.73; p < 0.001); death (HR 0.49; 95% CI, 0.41–0.57; p < 0.001) and hHF or death (HR 0.54; 95% CI, 0.48–0.60; p < 0.001). In OBSERVE-4D, 142,800 new users of canagliflozin, 110,897 new users of other SGLT2is, and 460,885 new users of non-SGLT2is were identified [32]. The study showed a HR for hHF with canagliflozin vs non-SGLT2i of 0.39 (95% CI, 0.26–0.60). Finally, in EMPRISE, after propensity-score matching, 16,443 patient pairs who initiated empagliflozin or sitagliptin were identified. The study showed that, compared with

Table 2 – Cardiovascular outcomes in major trials with GLP-1 receptor agonists.

	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND	PIONEER-6
Drug tested	Lixisentide	Liraglutide	Semaglutide	Exenatide OW	Albiglutide	Dulaglutide	Oral Semaglutide
Subjects, n	6,068	9,340	3,297	14,752	9,463	9,901	3,183
Duration of follow-up	2.1 years	3.8 years	2.1 years	3.2 years	1.6 years	5.4 years	1.3 years
Baseline HbA1c, %	7.7	8.7	8.7	8.0	8.7	7.3	8.2
Cardiovascular risk, %	100	81.3	58.8	73.1	100	31.4	84.6
Main cardiovascular outcomes HR (95%CI)	Primary outcome 3P-MACE 1.02 (0.89–1.17) Non-inferior to placebo	Primary outcome 3P-MACE 0.87 (0.78–0.97) NNT = 53	Primary outcome 3P-MACE 0.74 (0.58–0.95) NNT = 44	Primary outcome 3P-MACE 0.91 (0.83–1.00) Non-inferior to placebo	Primary outcome 3P-MACE 0.78 (0.68–0.90) NNT = 50	Primary outcome 3P-MACE 0.88 (0.79–0.99) NNT = 72	Primary outcome 3P-MACE 0.79 (0.57–1.11) Non-inferior to placebo
Composite renal outcome measure including macroalbuminuriaHR (95%CI)	0.84 (0.68–1.02) –	0.78 (0.67–0.92) NNT = 67	0.64 (0.46–0.88) NNT = 44	0.88 (0.76–1.01) –	Not reported	0.85 (0.77–0.93) NNT = 38	Not reported

3P- MACE: 3-point major adverse cardiovascular events; NNT: number needed to treat.

sitagliptin, empagliflozin decreased the risk of hHF by 50% (HR, 0.50; 95% CI, 0.28–0.91) over a mean follow-up of 5.3 months [33]. Altogether, these studies show that treatment with SGLT2is as compared to other glucose-lowering drugs is associated with a significantly lower risk of hHF, suggesting that the benefits seen with CVOTs may be a class effect applicable to a broad population of T2DM patients.

Heart failure is a heterogeneous condition encompassing at least two major categories: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). To which extent SGLT2is could exert a similar effect in both conditions is still a matter of active evaluation. Calculation of the number needed to treat (NNT) in DECLARE [34] seems to suggest a more evident beneficial effect in T2DM subjects with HFrEF (Fig. 1). This was, at least initially, confirmed by the results of the Dapa-HF study [35]. In 4,744 individuals with HF and ejection fraction <40%, those randomized to dapagliflozin had a 26% risk reduction of worsening heart failure (i.e. hospitalization or urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death (HR 0.74; 95%CI, 0.65–0.85; $p < 0.001$). Of relevance, the study included individuals with and without diabetes and the favorable findings were similar in both groups, stressing the concept that the beneficial effect on HF is an intrinsic feature of SGLT2is.

4. Stroke

In the EMPA-REG trial the HR for stroke was 1.18 (95% CI, 0.89–1.56; $p = 0.26$) [18]. This unfavorable trend was primarily due to 18 patients in the empagliflozin group with a first event >90 days after last intake of study drug. When only events occurring during treatment or ≤90 days after last dose of drug were considered, the HR decreased to 1.08 (95% CI, 0.81–1.45; $p = 0.60$) [36]. In no case, however, empagliflozin could be considered to impact on the risk of fatal and nonfatal stroke. Such a neutral effect was confirmed in CANVAS (HR 0.90; 95% CI, 0.71–1.15) [19] and DECLARE (HR 1.01; 95% CI, 0.84–1.21) [20]. On the contrary, a beneficial effect of GLP1-RAs has been documented in almost all CVOTs. The meta-analysis by Barkas et al. [37] included 4 of the 7 completed CVOTs using GLP1-RAs and showed a relative risk reduction for nonfatal (HR 0.88; 95% CI, 0.78–0.99) and fatal (HR 0.84; 95% CI, 0.60–1.17) stroke. The inclusion of all GLP1-RA CVOTs [29] only reinforced this finding with a relative risk reduction of 16% for fatal and nonfatal stroke (HR 0.84; 95% CI, 0.74–0.93). Finally, Lim and associates [38] have shown how this beneficial effect of GLP1-RAs may be shared by thiazolidinediones but not by SGLT2i nor DPP4i.

5. Renal outcomes

Another point of distinction between these two classes of novel glucose-lowering agents is represented by the renal outcomes. That SGLT2is could have a favorable effect on renal outcome was already apparent in EMPA-REG [18] where, after an initial drop, eGFR remained constant over the time as opposed to a progressive decline in the placebo group. When the slopes of eGFR where considered, empagliflozin was found to reduce eGFR (change per week, ml/min per

1.73 m^2) on treatment initiation (empagliflozin: −0.77; 95% CI, −0.83 to −0.71; placebo: 0.01; −0.08 to 0.10; p < 0.001) although annual mean slope did not decline with empagliflozin during chronic treatment (empagliflozin: 0.23; 0.05 to 0.40; placebo: −1.46; −1.74 to −1.17; p < 0.001) [39]. Incident or worsening nephropathy, defined as progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease also occurred in fewer patients assigned to EMPA (HR 0.61; 95% CI, 0.53–0.70; p < 0.001) [40]. In CANVAS [19] progression of albuminuria occurred less frequently in subjects treated with CANA (HR 0.73; 95% CI, 0.67–0.79), and regression of albuminuria was more common (HR 1.70; 95% CI, 1.51–1.91). Moreover, the composite outcome of sustained 40% reduction in eGFR, the need for renal-replacement therapy, or death from renal causes occurred less frequently among participants in the CANA group than among those in the placebo group [19]. In DECLARE the incidence of the renal composite outcome was 4.3% in the DAPA group and 5.6% in the placebo group (HR 0.76; 95% CI, 0.67–0.87) [20] in line with the results of EMPA-REG OUTCOME and CANVAS. Of relevance, the beneficial effect of SGLT2i on a renal endpoint encompassing renal worsening, end-stage renal disease and death for renal cause was independent of initial renal function. In the meta-analysis of Zelniker et al. [30] the relative risk reduction was 33% (HR 0.67; 95% CI, 0.51–0.89) in T2DM individuals with eGFR < 60 ml/min per 1.73 m^2, 44% (HR 0.56; 95% CI; 0.46–0.70) in those with eGFR 60–90 ml/min per 1.73 m^2 and of 56% (HR 0.44; 95% CI, 0.32–0.59) in those with normal eGFR, i.e. > 90 ml/min per 1.73 m^2. Although these beneficial effects of SGLT2is are mainly derived from secondary endpoints of CVOTs, a direct confirmation comes from a dedicated trial, the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial [41]. This was a double blind, randomized trial that assigned patients with T2DM and albuminuric chronic kidney disease to receive CANA (100 mg daily) or placebo [41]. The primary outcome was a composite of end-stage kidney disease (dialysis for at least 30 days, kidney transplantation, or an eGFR of <15 ml/min per 1.73 m^2), doubling of the serum creatinine level from baseline, or death from renal or CV disease. In this specific population, the relative risk of primary outcome was 30% lower with CANA than with placebo (HR 0.70; 95% CI, 0.59–0.82; p = 0.00001). The CANA group also had a lower risk of CV death, myocardial infarction or stroke (HR 0.80; 95% CI, 0.67–0.95; p = 0.01) and hHF (HR 0.61; 95% CI, 0.47–0.80; p < 0.001) [41].

A renal protection has been claimed to be exerted by GLP1-RAs as well. A further analysis of LEADER [42] showed that the renal outcome (a composite of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, end-stage renal disease, or death due to renal disease) occurred in fewer participants in the LIRA group than in the placebo group (HR 0.78; 95% CI, 0.67–0.92; p = 0.003). The largest effect was reduction in persistent macroalbuminuria (HR 0.74; 95% CI, 0.60–0.91; p = 0.004) with no apparent effect on harder renal outcomes [42]. The REWIND study evaluated, as a secondary outcome, a composite microvascular endpoint including a renal component, defined as first occurrence of new macroalbuminuria, sustained decline in eGFR of 30% or more from baseline, or chronic renal replacement therapy [43]. During a median follow-up of 5.4 years, the renal outcome developed in 17.1% of participants in the dulaglutide group and in 19.6% of those in the placebo group (HR 0.85; 95% CI, 0.77–0.93; p = 0.0004) with a more evident effect for new macroalbuminuria (HR 0.77; 95% CI, 0.68–0.87; p < 0.0001) [43]. When all available data have been pooled and meta-analyzed a 17% statistically significant relative risk reduction in the composite renal endpoint including macroalbuminuria (HR 0.83; 95% CI, 0.78–0.89; p < 0.0001) was found [29]. However, when only renal function was considered this reduction was attenuated to a non-significant 13% (HR 0.87; 95% CI, 0.73–1.03; p = 0.098) [29]. When the renal effect of GLP1-RAs and SGLT2i were compared, the former were found to reduce renal endpoints including macroalbuminuria by 18% (HR 0.82; 95% CI, 0.75–0.89) as compared to a 38% reduction (HR 0.62; 95% CI, 0.58–0.67) with the latter. This difference becomes even more apparent when macroalbuminuria is not considered (GLP1-RAs: HR 0.92; 95% CI, 0.80–1.06; SGLT2i: HR 0.55; 95% CI, 0.48–0.64) [28]. In summary, GLP1-RAs and SGLT2is reduce the risk of MACE to a similar degree in patients with established CV disease with a more apparent effect of GLP1-RAs on fatal and nonfatal stroke whereas SGLT2is exhibit greater reduction of the risk for hospitalization for HF and progression of kidney disease. These distinct clinical benefits should be considered in the decision-making process when treating T2DM patients.

6. Matching SGLT2is and GLP1-RAs to patient's needs

The different profile of cardio-renal protection of these two classes of glucose lowering agents has already translated in many current guidelines for the treatment of T2DM. The guidelines indeed identify specific categories of T2DM, where specific categories of T2DM subjects in whom the use of one or the other class of drugs should be preferred. A typical example is represented by the Consensus Report on the Management of Hyperglycemia in type 2 diabetes by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [44]. On the basis of the results of the CVOTs that we have briefly summarized above, this report, along with its most recent revision [45], recommends treating high CV risk individuals with a GLP1-RA or SGLT2i to reduce major adverse CV events, hospitalization for heart failure, CV death or chronic kidney disease (CKD) independently of baseline HbA1c or individualized HbA1c target. In other words, because of the properties of these agents, the goal of pharmacologic therapy is not just ensuring individualized glycemic control but also addressing organ damage in a more direct manner [46] as recommended with great emphasis by the recent Guidelines on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) [47]. The ADA/EASD Consensus Report also invite considering GLP-1RAs in T2DM patients without established CV disease but who have indicators of high CV risk [45]. Finally, SGLT2is are recommended in T2DM patients with HF, particularly those with HFrEF to reduce hHF, MACE and CVD death, as well as in CKD patients (eGFR 30 to ≤60 ml/min per 1.73 m^2 or

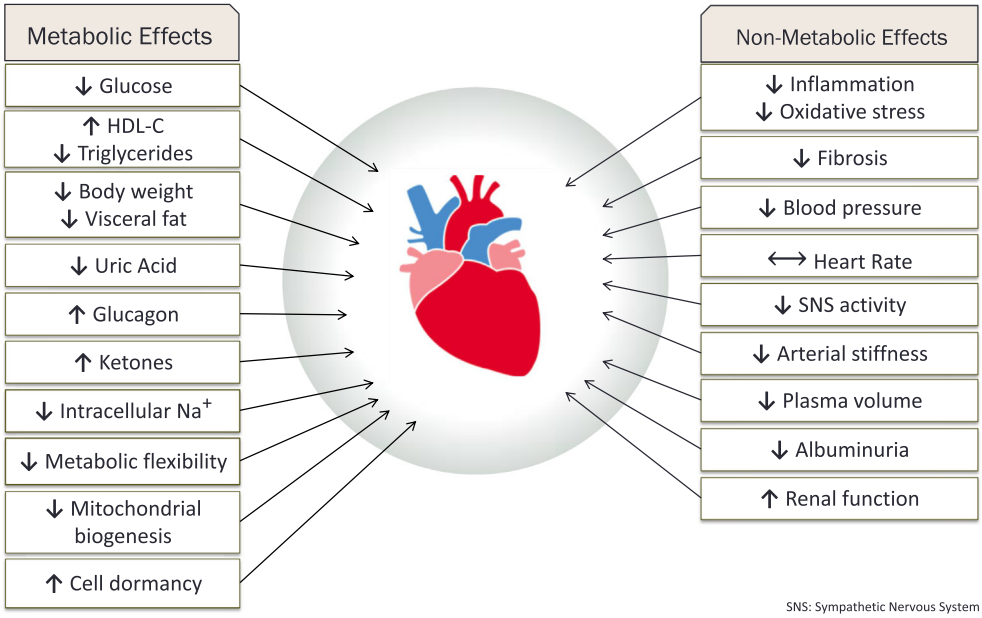

Fig. 1 – Potential mechanisms for the beneficial effect of SGLT2-inhibitors on cardiovascular outcomes.

urinary albumin-to-creatinine ratio >30 mg/g, particularly >300 mg/g) to prevent the progression of CKD, hHF, MACE and CV death.

All these indications are based on the specific benefits evidenced in the CVOTs. However, other elements could contribute to the identification of those T2DM patients who may be more responsive to the treatment. Thus, one could consider the need for addressing specific pathophysiologic mechanisms accounting for CV risk or progression of renal failure. This will require a better understanding of the main target of the beneficial effects of SGLT2is and GLP1-RAs.

7. Mode of action of SGLT2is and GLP1-RAs

The CV benefit conferred by SGLT2is and GLP1-RAs is unlikely to recognize similar mechanisms of action. This is readily apparent by comparing the timing for these benefits to become apparent. For instance, while in the EMPA-REG trial [18], the curves for MACE started opening up already after the first 6 months of treatment, this required longer time (12–18 months) in LEADER [21].

The rapid effect of SGLT2is has been claimed to recognize a hemodynamic effect with improvement in ventricular loading conditions through a reduction in preload (secondary to natriuresis, osmotic diuresis) and afterload (reduction in blood pressure and improvement in vascular function) [48]. Improvement of cardiac metabolism and bioenergetics, myocardial Na^+/H^+ exchange inhibition, reduction of necrosis and cardiac fibrosis, favorable effect on adipokines and cytokines and decreased epicardial adipose tissue mass have been also suggested to contribute to CV protection [48]. Finally, restoration of the tubulo-glomerular feedback and amelioration of circulating volume control has been suggested as a central mechanism by some authors [49]. More recently it has been hypothesized that the cardioprotective effects of SGLT2i may be related to their ability to switch cell life programming from a defense to a dormancy state [50]. Fig. 1 summarizes all potential CV protective mechanisms.

As per the SGLT2is also for GLP-1RAs the favorable effects on CV outcomes are likely to be multifactorial [51]. Among the potential mechanisms are the effects on diabetes parameters (glycemic control, low risk of severe hypoglycemia), on CV risk factors (body weight, blood pressure, lipoproteins/lipids), and an interaction with GLP-1 receptors in the CV system. The latter has been suggested to result in improved endothelial function/vasodilation, cardiac function under coronary ischemia, and anti-inflammatory/anti-atherosclerotic effects. Altogether, GLP1-RAs are believed to exert an anti-atherosclerotic effect, which would account for the longer time required before translation into reduction of CV events. From this brief description, it should be apparent how the delineation of the mechanisms underlying the CV benefit of these agents may be quite relevant for the identification of those subjects who may benefit most from the use of one or the other agent. Of interest, the main mechanisms potentially accounting for CV protection of these two classes of agents are so different to be potentially complementary, making their combination an attractive form of treatment [52] that should be tested in dedicated CVOTs.

8. What else should we consider for patient selection?

The final goal of a treatment is to provide the largest benefit while reducing as much as possible side effects. Therefore, appreciation of the safety and tolerability profile may also contribute in profiling the ideal patients for SGLT2is or GLP1-RAs therapy. The most common adverse event observed with SGLT2is is represented by genital mycotic infections, particularly in females [53], and to a lesser extent urinary tract infections. A relatively rare though serious complication associated with SGLT2is is the development of an euglycemic

diabetic ketoacidosis (DKA) [54]. Nonetheless, a recent meta-analysis of randomized controlled trials showed that, if SGLT2is are properly prescribed, the risk of DKA is negligible [55]. A higher risk of bone fractures and lower limb amputations has been reported in CANVAS trial [19] though such an increased risk has not been confirmed in CREDENCE [41]. It is also advisable avoiding the use of these agents in patients with osteoporosis or at risk of falls. In the EMPA-REG Outcome [18] and DECLARE [20] trials no adverse events related to volume depletion were reported despite the large concomitant use of diuretics. Nonetheless, in the CANVAS trial more symptoms related to osmotic diuresis (34.5 vs 13.3 events/1000 patient-years) and volume depletion (26.0 vs 18.5 events/1000 patient-years) were reported in patients treated with canagliflozin [19]. The incidence of bladder cancer as well as of any other type of cancer appears to be not significantly increased by treatment with any SGLT2i [56]. Recently, the FDA has released a Drug Safety Communication regarding the occurrence of 12 cases of Fournier's gangrene associated with treatment with SGLT2is [57].

Gastrointestinal effects, including nausea (~15–20%), vomiting (~5%) and constipation (~5%) are the most frequently reported adverse events occurring with administration of GLP1-RAs [58,59]. Although these agents have been initially thought to increase the risk of pancreatitis and pancreatic cancer, a recent meta-analysis reported that the incidence of these conditions is not different from the one observed with comparators [60]. GLP1-RAs can stimulate calcitonin release, up-regulate calcitonin gene expression, and C-cell hyperplasia in murine models [61] but no differences in the risks of thyroid cancer has been found [62]. Therapy with GLP-1RAs seems to be associated with an increased risk of bile duct and gallbladder disease [63]. In SUSTAIN 6 trial, semaglutide was associated with a higher rate of worsening retinopathy [22]; however, this unexpected result may be attributed to the magnitude and rapidity of HbA1c reduction during the initial 16 weeks of treatment in patients with diabetic retinopathy at baseline [64]. In the FDA Adverse Event Reporting System (FAERS) database there was no evidence of retinopathy progression [65]. Moreover, the AngioSafe type 2 diabetes study has provided experimental and clinical data to confirme no effect of GLP1-RAs on angiogenesis and or association with severe diabetic retinopathy [66]. In summary, safety and tolerability profiling of SGLT2is and GLP1-RAs should be considered for any subjects in whom one or the other could be deemed more appropriate on the basis of the expected benefit. A correct balance between indication and tolerability is indeed the most reliable index for treatment adherence.

9. Conclusion

After decades of stagnation, in the past 20 years there has been steady introduction of new glucose-lowering agents and, currently, there are up to 13 classes of drugs. Two of these classes have shown in large randomized clinical trial to provide CV and renal protection. Though this is an extraordinary achievement, it raises the clinical challenge of how to choose the right medication in the right patient in the attempt to providing sustained targeted therapeutic efficacy with the goal of reducing the burden of long-term complications. Unfortunately, this process is still largely based on empirical ground. The future may provide us with a more efficient care for T2DM thanks to the development of a diabetes

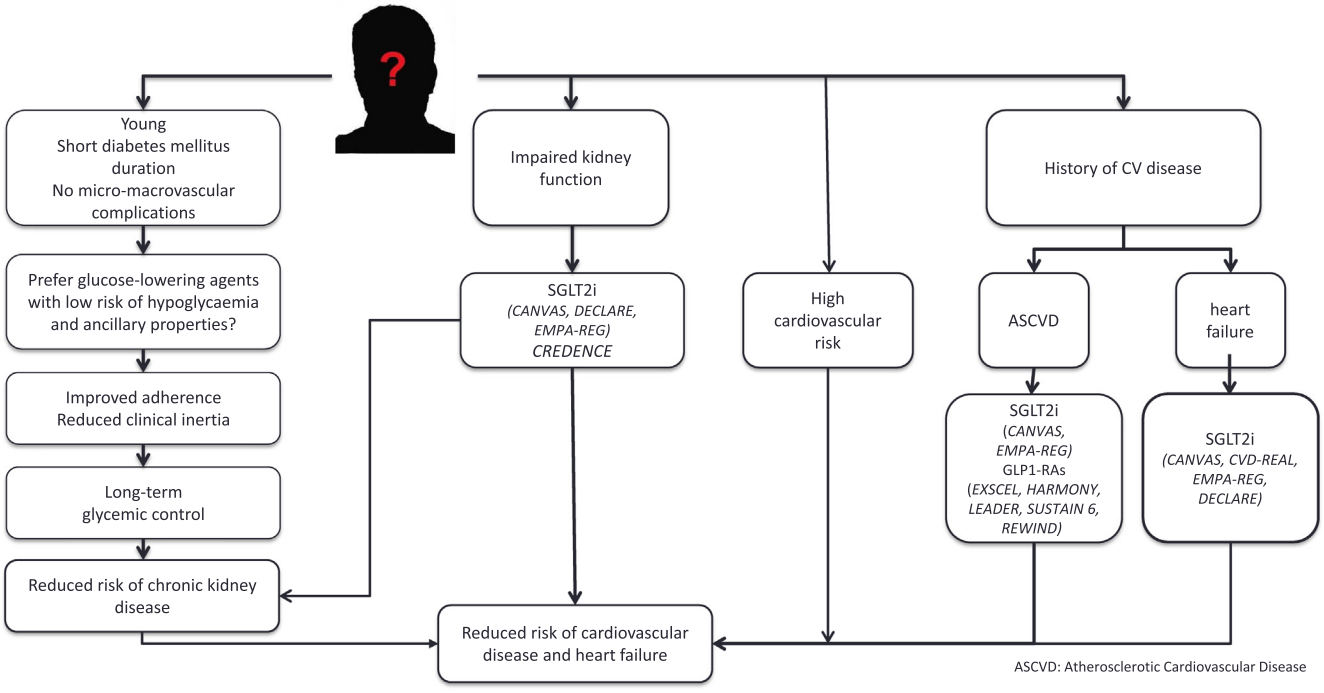

Fig 2 – Tentative treatment individualization on the basis of presence and absence of renal and cardiovascular complications as derived from the results of the Cardiovascular Outcomes Trials with SGLT2-inhibitors and GLP1 Receptor Agonists.

precision medicine [67]. In this transition time we should take advantage of the increasing bulk of evidence shedding more light in the complexity of the pathogenesis of T2DM and more solid data coming from rigorous large CVOTs.

An example of this process is represented in Fig. 2. According to this approach, a distinction can be made on the basis of presence or absence of high CV risk, a known positive history of CV disease. And or the stage of renal function. In young patients facing a long duration of the disease, in those with newly diagnosed T2DM and those free of micro- and macrovascular complications immediate and sustained glycemic control should be pursued. Strict glycemic control, indeed, remains the most effective therapeutic measure to reduce the risk of micro-vascular complications. Moreover, the pathophysiology of micro- and macro-vascular damage does recognize much commonality than usually thought [68,69] suggesting prevention of micro-vessel disease may, in the long term, result in less macro-vascular complications as well. In line with this view are the results of studies showing that the risk of CV disease and mortality increases with the number of micro-vascular complications [70]. In ensuring glycemic control glucose-lowering agents with low risk of hypoglycemia and favoring no change, if not loss of body weight should be preferred because avoiding side effects may favor patient's adherence to treatment and reduce physicians' clinical inertia contributing to the chance of successful therapy. The main element for decision making here is only related to the glucose target with the expectation that this may result in reducing the risk of long-term diabetic complication. This approach, however, may be changing in the future as some medication have shown to exert effects beyond glucose control. An example is the potential effect of SGLT2i on renal protection shown in T2DM patients with CV disease with empagliflozin [39] and in a population including people with milder CV risk with canagliflozin [40] and even more in DECLARE [20]. In particular, what may support an early introduction of these agents is the observation that a renal protection is appreciated also in people with normal eGFR [28]. If this effect will be confirmed by dedicated studies, early introduction of these agents in treatment of T2DM may lend even stronger protection and significant delay of the development of dreadful complications. Another example is represented by a T2DM subjects with diabetic kidney disease. This is the typical patient included in CREDENCE [41], where canagliflozin was shown to reduce progression of the renal disease, risk of MACE and hospitalization for HF. In line with this, current guidelines recommend the use of a SGLT2i for T2DM patents with diabetic kidney disease [44,45]. The third example is that of the T2DM patient with established CV disease. In this case, guidelines recommend distinguishing between those with an atherosclerotic CV disease from those HF. For the former, a GLP1-RA or a SGLT2i with proven CV benefit should be considered although if stroke prevention is the main goal of treatment a preference could go for the GLP1-RAs. Conversely, for those subjects with a history of HF and in particular HFrEF a SGLT2i should be preferred. With two classes of drug with proven CV protection it might be possible in the near future to consider assessing the potential of combination therapy not only with respect to glucose-lowering efficacy and persistence but also regarding the potential for an even stronger and wider CV protection. Though this is an optimistic scenario, the clinician will still have to face the usual problem of selecting the right medication (and the best combination) for the right patient. While we wait for better educated treatment strategies based on careful patient's identification, the clinician must be able to appreciate the pros and cons of each

Table 3 – Pros and cons of SGLT2 inhibitors and GLP-1 receptor agonists.

	SGLT2 Inhibitors	GLP-1 Receptor Agonists
Pros	• Glycaemic improvement comparable to the most effective standard therapy • Weight loss • Blood pressure reduction • Negligible/low risk of hypoglycaemia • Cardiovascular protection • Renal protection • Generally well tolerated • Oral treatment	• Valuable efficacy profile • Weight loss • Blood pressure reduction • Negligible/low risk of hypoglycaemia • Cardiovascular protection • Renal protection (proven in LEADER trial) • Generally well tolerated • No increased risk for pancreatitis, pancreatic cancer or bone disease
Cons	• Increased risk of genital mycotic infections • Euglycaemic diabetic ketoacidosis (not confirmed in large trials) • Risk of dehydration and hypotension • Increased risk for lower-limb amputation and bone fractures (canagliflozin) • Rare occurrence of Fournier's gangrene • Increased risk of bladder cancer (dapagliflozin warning), and on any type of cancer (?) • Not recommended or contraindicated in severe chronic kidney disease • Cost	• Less HbA1c lowering with short-acting agents • Gastrointestinal effects • Injectable therapy • Contraindicated in personal/family history of medullary thyroid cancer or MEN2 • Higher rate of worsening retinopathy (SUSTAIN-6) • Increased risk of bile duct and gallbladder disease • Not recommended or contraindicated in moderate to severe chronic kidney disease (exenatide and lixisenatide) • Cost

individual medication (Table 3) as well as, the individual need along with patient's understanding, expectation, and collaboration as advocated in the most recent ADA/EASD position statement on the treatment of hyperglycemia in T2DM [44,45].

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