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Cardio-Renal Benefits of GLP-1 Receptor Agonists vs. SGLT-2 Inhibitors in Type 2 Diabetes: Are They Juxtaposed?

Both glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose co-transporter-2 inhibitors (SGLT2i) have taken center stage in the management of type 2 diabetes (T2D) having a compelling indication in the presence of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF) with reduced (HFrEF) as well as preserved ejection fraction (HFpEF), and chronic kidney disease (CKD). The 2022 joint position statement of the American Diabetes Association (ADA) and the European Association of Study in Diabetes (EASD) preferred SGLT2i over GLP-1RA in presence of HF and albuminuric CKD, while either GLP-1RA or SGLT2i may be chosen in people with high cardiovascular (CV) risk or established ASCVD or non-albuminuric CKD without any preference between the two classes of antidiabetic drugs. Both these classes of drugs have been recommended independently of baseline HbA1c, individualized HbA1c target, or background metformin use [1]. Importantly, despite the proven cardio-renal benefits with both GLP-1RA and SGLT2i that led first ADA-EASD consensus recommendation of using either agent in 2018 [2], worldwide clinical inertia still appears to exist with regard to its use with only a modest increase over time [3].

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In this issue of *Clinical Diabetology*, Rajput and colleagues have critically reviewed the GLP-1RA use in the context of routine clinical practice in India. While a group of eight experts has opined on using GLP-1RA upfront in people with T2D with high CV risk or established ASCVD, CKD or HF, they have also proposed oral semaglutide as the first-line therapy for T2D in Asian Indians [4]. Although GLP-1RA could be helpful in Asian Indians given the higher proportion of central obesity and higher risk of premature CV diseases, such trade-off should also need to be made in the context of lower body mass index and thin limbs in Asian Indians compared to the Caucasians [5]. Similarly, while a meta-analysis [6] reported larger ASCVD benefits with GLP-1RA in Asians compared to Whites and another meta-analysis [7] showed exaggerated ASCVD benefits with GLP-1RA in Asians compared with SGLT2i, these findings cannot be extrapolated to South Asians or Indians in absence of dedicated studies. Indeed, CV benefit with GLP-1RA in people with high CV risk or established ASCVD is irrefutable; however, the role of GLP-1RA for CKD and HF prevention in T2D is inconsistent and far below the benefits observed with SGLT2i. Moreover, there is neither any data with GLP-1RA for HF reduction in people with established HF nor any data currently available for the GLP-1RA for the CKD progression reduction in people with established CKD (clinical trials are ongoing in this area; FLOW [NCT03819153], REMODEL [NCT04865770], RAISE-KT [NCT04741074]). Furthermore, proposing oral semaglutide as first-line therapy in Asian Indians with T2D to improve cardio-renal outcomes seems provocative in the absence of

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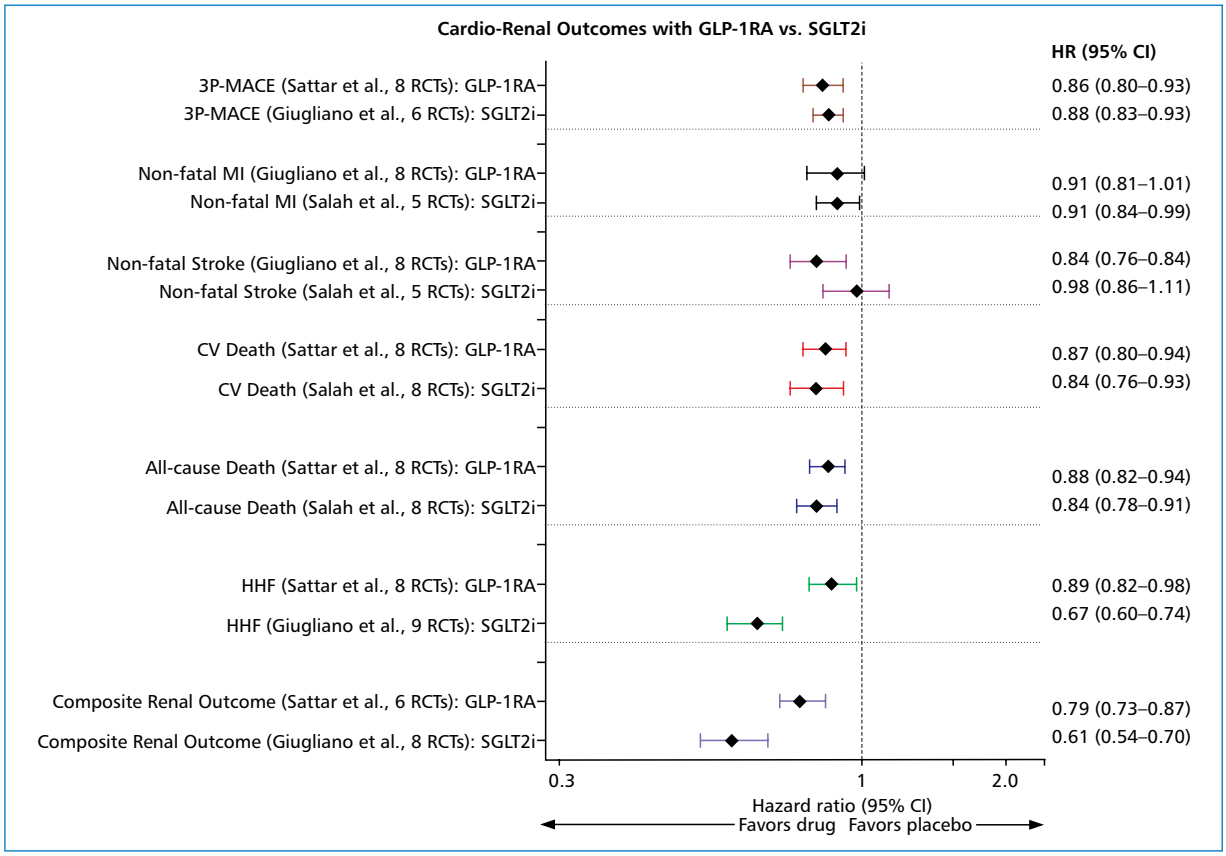

Figure 1. Cardio-Renal Outcomes with GLP-1RA vs. SGLT2i [9–13]
CI — confidence interval; CV — cardiovascular; GLP-1RA — glucagon-like peptide-1 receptor agonists; HHF — heart failure hospitalization; MACE — major adverse cardiovascular events; MI — myocardial infarction; RCT — randomized clinical trial; SGLT2i — sodium-glucose co-transporter-2 inhibitors

any positive CV outcome trials at the moment (PIONEER-6 [NCT02692716] was neutral and ongoing SOUL [NCT03914326] is under progress). Notwithstanding, any country-specific propositions should have been made in the context of other available cheaper agents that has similar cardio-renal benefits. This is especially important in the context of India where a cheaper generic version of SGLT2i dapagliflozin is widely available and the per-day cost is at least 40-times cheaper than oral semaglutide or injectable GLP-1RA. It should be recalled that even the latest National Institute of Clinical Excellence (NICE), UK, 2022 guideline has put SGLT2i much higher in the hierarchy along with metformin in people with T2D having high CV risk, keeping GLP-1RA much lower in order, primarily due to cost-benefit evaluation [8].

Nevertheless, this raises a few important questions – a) How comparable are cardio-renal benefits exerted by GLP-1RA and SGLT2i in the absence of any head-to-head randomized controlled trials?, b) Does absolute cardio-renal benefit differ between these two classes of drugs?, c) What is the evidence available from the real-world studies that compared cardio-renal outcomes with these two classes of drugs?, and, d) What is the cost-benefit analysis of two classes of drugs? To find out the answer we pooled the results from all recently conducted systematic reviews, meta-analyses, and network meta-analyses of both GLP-1RA and SGLT2i [9–16]. Overall, the cardio-renal benefits of GLP-1RA and SGLT2i are juxtaposed and comparable (Fig. 1) [9–13]. With the emergence of GLP-1RA trial results, the gap between the two classes of drugs seems to be narrowing and gradually leveling off [17]. However, some caveats still remain while interpreting these results that appear to be similar (Fig. 2). Notwithstanding, two distinct differences are noticeable between the two drug classes. While stroke benefit is quite appreciable with GLP-1RA but not with the SGLT2i; reduction in hospitalization due to HF (HHF) and composite renal outcome are distinctly larger with SGLT2i compared with GLP-1RA. On an individual level, the SGLT2i class has confirmed benefits in – i) people with T2D, ii) with CKD (with or without T2D), and iii) in patients with HFrEF or HFpEF (with or without T2D) (Fig. 3). SGLT2i has additionally

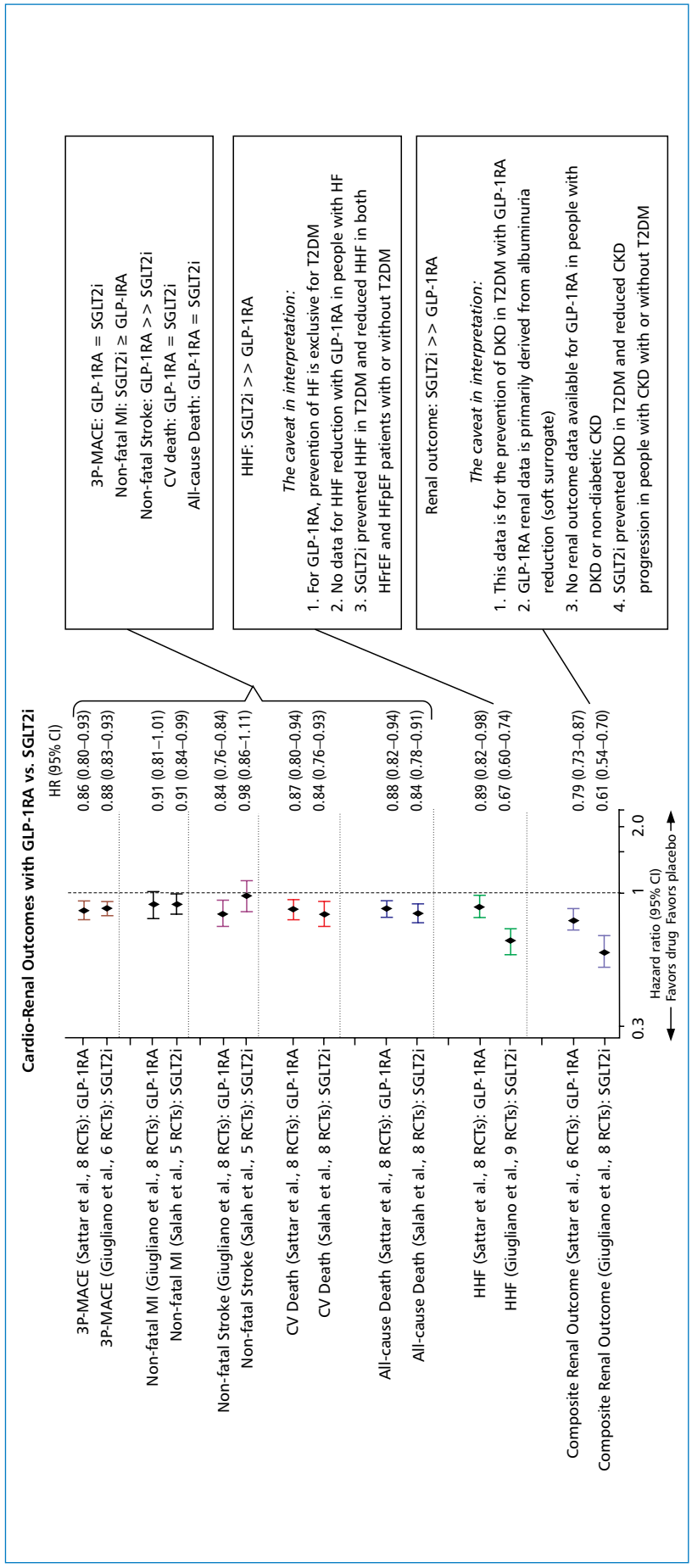

Figure 2. Interpretation of Data from Cardio-Renal Outcome Trials of GLP-1RA vs. SGLT2i
CKD — chronic kidney disease; CV — cardiovascular; DKD — diabetic kidney disease; GLP-1RA — glucagon-like peptide-1 receptor agonists; HFpEF — heart failure with preserved ejection fraction; HFrEF — heart failure with reduced ejection fraction; HHF — heart failure hospitalization; MACE — major adverse cardiovascular events; MI — myocardial infarction; RCT — randomized clinical trial; SGLT2i — sodium-glucose co-transporter-2 inhibitors; T2DM — type 2 diabetes mellitus

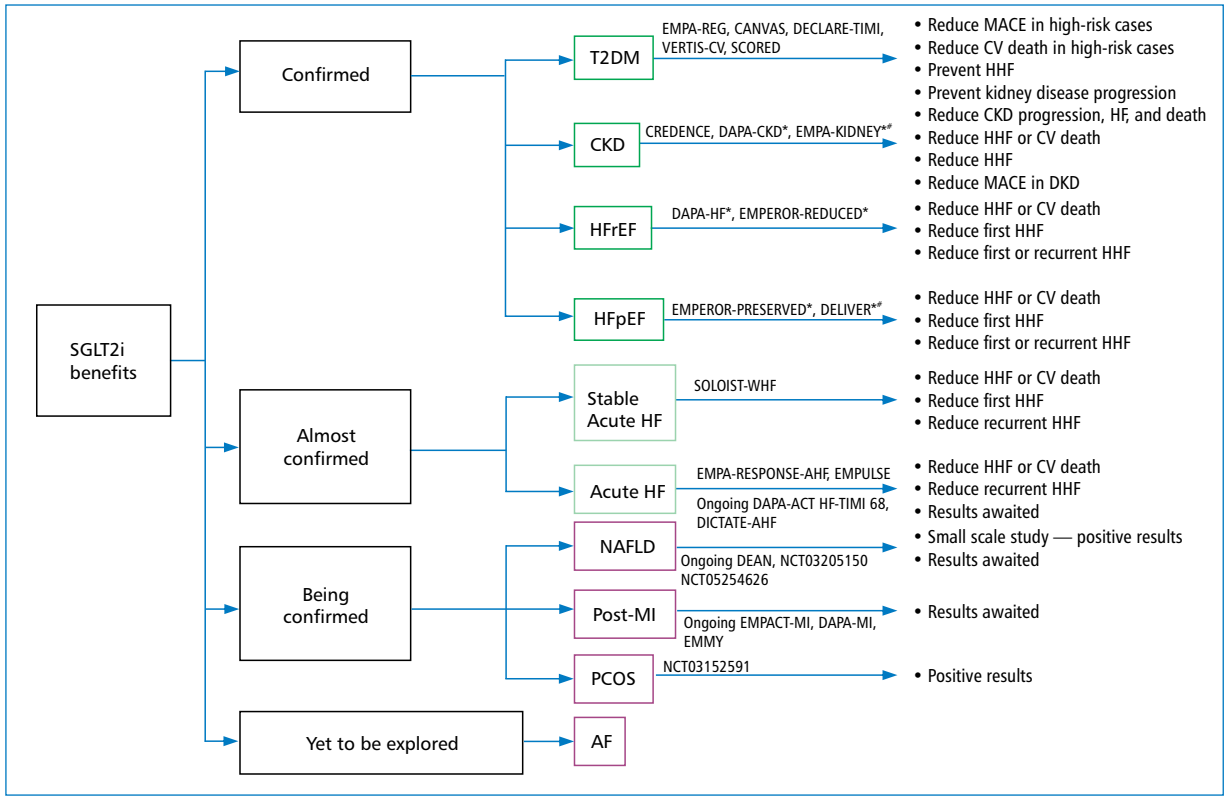

Figure 3. Randomized Controlled Trials of SGLT2i
*With or without T2DM, #Positive top-line results
AF — atrial fibrillation; CKD — chronic kidney disease; CV — cardiovascular; HF — heart failure; HFpEF — heart failure with preserved ejection fraction; HFrEF — heart failure with reduced ejection fraction; HHF — heart failure hospitalization; MACE — major adverse cardiovascular events; MI — myocardial infarction; NAFLD — non-alcoholic fatty liver disease; PCOS — polycystic ovarian syndrome; SGLT2i — sodium-glucose co-transporter-2 inhibitors; T2DM — type 2 diabetes mellitus

been found to be useful in the setting of acute HF and is already included in the routine guideline-directed medical therapy (GDMT) for the treatment of stable acute heart failure. Indeed, the 2022 joint committee of the American Heart Association, American College of Cardiology, and the Heart Failure Society of America guidelines recommends SGLT2i for HF prevention in patients with T2D for both primary (Class 1, Level of evidence A) and secondary prevention in those having HFrEF (Class 1, Level of Evidence A) or HFpEF (Class 2, Level of Evidence B) regardless of T2D [18]. Further ongoing trials will finally confirm the actual potential of SGLT2i in the setting of acute HF including myocardial infarction (MI). Comparatively, GLP-1RA class has confirmed cardiac benefits only in people with T2D (Fig. 4). The benefits of GLP-1RA on composite renal endpoints in T2D are primarily derived from albuminuria reduction, and worsening of kidney function has been just nominal (hazard ratio 0.86; 95% confidence interval, 0.72–1.02; p = 0.09) in a pooled meta-analysis of all GLP-1RA trials [11]. Similarly, reduction in HHF with GLP-1RA is inconsistent. Indeed, reductions in HHF were observed only in two trials – of albiglutide (HARMONY) and efpeglenatide (AMPLITUDE-O) and thus earlier meta-analyses that did not include these two trials [19] found no significant benefit in HHF with GLP-1RA. Finally, there are no studies yet available for GLP-1RA in CKD or HF. The largest network meta-analyses (764 trials; 421,346 patients) conducted to date that assessed the cardio-renal benefit of GLP-1RA and SGLT2i found both classes of drugs lowered non-fatal MI, CV death, all-cause death, and kidney failure significantly but the absolute benefits between these two drug classes vary substantially based on CV and renal risk profile. Notably, in all risk categories, the absolute benefit with SGLT2i appeared larger than the GLP-1RA but it was quite distinct with increasing CV and renal risk. The quantum of absolute benefit with SGLT2i was 1.5-times larger than GLP-1RA in people having high or very high CV or renal risk [14]. This finding is consistent with a previous network meta-analysis that claimed SGLT2i to be superior and the drug class of choice compared to GLP-1RA in terms of cardio-renal benefits including death reduction [15]. One consistent differential finding that emerged

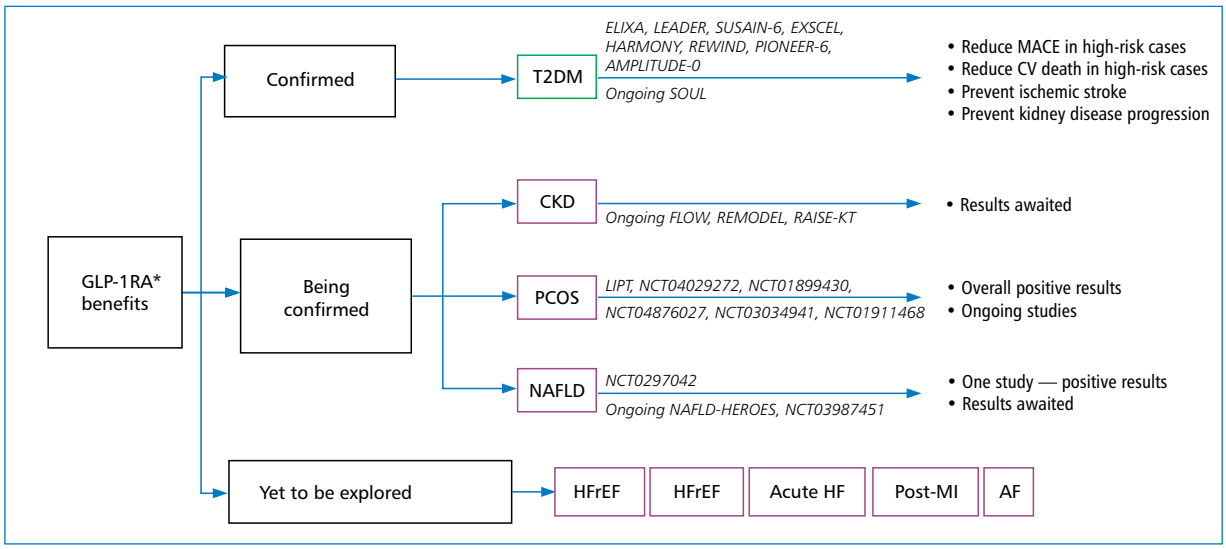

Figure 4. Randomized Controlled Trials of GLP-1RA
*Approved antidiabetic doses
AF — atrial fibrillation; CKD — chronic kidney disease; CV — cardiovascular; GLP-1RA — glucagon-like peptide-1 receptor agonists; HF — heart failure; HFpEF — heart failure with preserved ejection fraction; HFrEF — heart failure with reduced ejection fraction; MACE — major adverse cardiovascular events; MI — myocardial infarction; NAFLD — non-alcoholic fatty liver disease; PCOS — polycystric ovarian syndrome; T2DM — type 2 diabetes mellitus

from all recent large-scale network meta-analyses is significant reduction in non-fatal stroke with GLP-1RA compared to SGLT2i (no benefit) [14–16], while HHF reduction [14–16] and renal outcomes were [15, 16] significantly larger with SGLT2i compared to GLP-1RA.

Several recent real-world head-to-head studies have evaluated the cardio-renal outcomes between GLP-1RA and SGLT2i. A real-world study from Rome, Italy evaluated the 10-year risk for coronary heart disease (CHD) and reported both GLP-1RA and SGLT2i reduced the 10-year risk for CHD in T2D for primary prevention using UKPDS-Risk Engine [20]. Another Italian study reported a significantly lower risk of MACE (primarily due to a reduction in MI) with SGLT2i compared to GLP1-RA, although no differences in stroke were observed between the two classes [21]. A propensity-matched primary prevention study from Sweden that compared MACE outcomes (at a median of 1.6 years) found no difference between the two classes of drugs, although SGLT2i users had increased risk (small absolute risk) of ischemic stroke compared to GLP-1RA [22]. Similar findings were noted in another Swedish Diabetes registry that showed a similar risk of MACE, CV death, and MI, although an increased risk of stroke for SGLT2i was observed compared to GLP1-RA [23]. However, in a nationwide Swedish registry-based cohort study, there was no difference in standardized 3-year risk for any CV outcomes (MI, stroke, HHF) including CV death between GLP-1RA vs SGLT2i [24]. Similarly, in ongoing EMPLACE (Cardiovascular and renal outcomes, and mortality in Danish patients with type 2 diabetes who initiate empagliflozin versus GLP-1RA), a Danish registry-based study, there was no difference in expanded MACE, HHF, or all-cause death between empagliflozin and liraglutide [25]. At least four real-world studies from US insurance or administrative database claims have also compared GLP-1RA and SGLT2i [26–29]. A retrospective cohort study from Texas showed similar CV outcomes between GLP-1RA vs SGLT2i, although only SGLT2i users had a lower risk of HHF [26]. A 5-year follow-up study found no difference in CV outcome between two classes of drugs in people with T2D having no CVD, although a significantly larger reduction in composite CV outcome and HHF was noted with SGLT2i compared to GLP-1RA in people having CVD [27]. Another US claims study found a significantly reduced risk of HHF for SGLT2i compared with GLP1-RA in older adults over a median follow-up of 6 months, with no difference in MACE or stroke [28]. The largest pooled analysis of 3 US claim databases reported SGLT2i users to have a lower risk of MI or stroke in patients with CVD compared with GLP-1RA users, and a significantly lesser risk of HF compared with GLP-1RA in people with T2D regardless of background CVD [29]. Finally, a healthcare utilization and cost analysis study from the US claims that compared GLP-1RA vs SGLT2i showed a significantly higher average per-person per-month cost difference for GLP-1RA compared to SGLT2i despite no difference

in composite CV outcomes. Moreover, significantly higher rates of patients on GLP-1RA were more likely to discontinue treatment, needed inpatient hospitalization and emergency department visits compared to SGLT2i [30].

Collectively, cardio-renal benefits with GLP-1RA and SGLT2i are nearly similar in people with T2D having high CV risk except for the prevention of stroke (better with GLP-1RA compared with SGLT2i), HHF (better with SGLT2i compared with GLP-1RA) and CKD progression (better with SGLT2i compared with GLP-1RA). SGLT2i has additional positive data in people with known CKD (reduced CKD progression) and HF (reduced HHF or CV death), with or without T2D. Such positive data is currently lacking with GLP-1RA. Importantly, SGLT2i is far cheaper compared to GLP-1RA in some countries including India and this makes SGLT2i a preferable class of drug over GLP-1RA in people with high CV risk including ASCVD, HF, and CKD.

Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship and take responsibility for the integrity of the work. They confirm that this paper will not be published elsewhere in the same form, in English or in any other language, including electronically.

Conflict of interest

Dr. Shah reports receiving research grants through the University of Colorado from NovoNordisk, Insulet, Tandem Diabetes Care, and Dexcom and honoraria from Dexcom, Insulet, LifeScan, DKSH Singapore, and Medscape LLC for consulting and speaking outside the submitted work. Dr. Singh has nothing to report.

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