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Review

Cardiovascular and renal outcomes with SGLT2 inhibitors: Real-life observational studies in older patients with type 2 diabetes SGLT2 inhibitors in elderly and real life

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SUMMARY

Patients with type 2 diabetes mellitus (T2DM) are exposed to a high risk of atherosclerotic cardiovascular disease, heart failure and chronic kidney disease. The incidence of these complications increases markedly with the duration of diabetes and aging. Sodium-glucose cotransporter 2 inhibitors (SGLT2is) showed a remarkable reduction in hospitalization for heart failure and progression of kidney disease in large prospective placebo-controlled trials. Post hoc analyses of these trials demonstrated that cardiorenal protection occurred independently of age. The present comprehensive review analyzes the effects of SGLT2is on cardiovascular and renal outcomes among older patients with T2DM in cohort studies and real-life conditions. SGLT2is were associated with a significant reduction in hospitalization for heart failure (alone or combined with mortality) and in a composite renal outcome, including end-stage renal disease when compared to other oral glucose-lowering drugs, dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists in patients aged ≥ 65 years and even ≥ 75 years. Several observational studies worldwide compared cardiorenal outcomes in people aged ≥ 65 years versus < 65 years and showed a similar relative benefit of SGLT2is in older versus younger patients with T2DM. These favourable results were obtained while the safety profile of SGLT2is in older patients was acceptable and almost comparable with that reported in younger patients. In conclusion, observational studies in real-life conditions confirm previous results reported in placebo-controlled trials and a positive benefit/risk balance in elderly patients with T2DM at risk of heart failure and chronic kidney disease.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) [1], heart failure (HF) [2] and chronic kidney disease (CKD) [3] are common complications in patients with type 2 diabetes mellitus (T2DM) and their prevalence increases with age and duration of diabetes. Therefore, it is crucial to prevent such complications in order to improve both the quality of life and life expectancy in an increasingly larger population of older patients with T2DM.

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) have demonstrated a marked reduction in hospitalization for heart failure (hHF), alone or combined with cardiovascular (CV) mortality, in patients with T2DM at high CV risk and in patients with HF [4–7]. Renal benefits were also reported in several RCTs in different populations [8,9]. The cardiovascular and renal benefits provided by SGLT2is have been observed whatever the age of the patients, with similar reduction in major CV adverse events (MACEs: a combination of CV death, nonfatal myocardial infarction and nonfatal stroke), hHF and renal outcomes as shown in post-hoc analyses of large prospective placebo-controlled trials that focused on the influence of age (review in [10]).

Whether these favourable results obtained in randomized controlled trials (RCTs) versus placebo are confirmed in real-life conditions when comparing SGLT2is users versus non-users treated with other antihyperglycaemic agents is less well known [11]. The present comprehensive review analyses the effects of SGLT2is on cardiovascular outcomes (MACES), hHF (alone or combined with CV death or all-cause death) and a composite renal outcome in patients with T2DM aged ≥ 60 years. Furthermore, when data are available, it compares outcomes among older versus younger patients (≥ 65 versus < 65 years or ≥ 75 versus < 75 years) in large cohort studies issued from different countries worldwide. Comparators were other oral glucose-lowering drugs (oGLD) or incretin-based therapies, either dipeptidyl peptidase-4 inhibitors (DPP-4is) or glucagon-like peptide-1 receptor agonists (GLP-1RAs). We will consider first cardiovascular efficacy, including the effect on hHF, and second the effects on a

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composite of renal endpoints combining a sustained reduction in estimated glomerular filtration rate (eGFR) and progression to end-stage renal disease (ESRD). Of course, real-world observational studies have some limitations and should always be interpreted with caution, even if the propensity score matching procedure was used in most studies to minimize the risk of biases between SGLT2i users versus non users. Most critical challenges encountered in designing and conducting such studies have been recently reviewed [12].

Cardiovascular efficacy of SGLT2is according to age

International literature provides two types of observational studies of potential interest: first, cohort studies carried out in elderly people (≥ 60 years as inclusion criteria, but most studies with patients ≥ 65 years) that compared CV outcomes in patients treated with SGLT2is versus those treated with another oGLD [13–22] (Table 1); second, subgroup analyses of cohort studies that compared CV outcomes in SGLT2i users versus non-users aged ≥ 65 years versus < 65 years [23–26] or aged ≥ 75 years versus < 75 years [13,16,17] (one study used 60 years as cut-of) [27] (Table 2).

Observational studies in T2DM patients older than 65 years

Studies were performed in different countries (US, UK, Canada, Scandinavia, Israel, Italy, Japan, South Korea) and SGLT2is were compared with different glucose-lowering agents: all types oGLD [14,20,22], DPP-4is [13,15-18], GLP-1RAs [17–19, [21]. (Table 1). Heterogeneous results across studies were reported for the effects on MACEs, all-cause mortality and CV mortality, some studies showing a significant reduction with SGLT2is versus comparators, others no significant change. In contrast, all studies that reported results on hHF (alone or combined with all-cause mortality) reported significant lower incidence rates with SGLT2is compared with oGLD [14,20,22] and DPP-4-is [13,15-18]. Results that compared SGLT2is with GLP-1RAs were less consistent, with a significant reduction in hHF in two studies [17,19] but only a non-significant trend in two others [18,21]. Overall, these results obtained in cohort patients aged > 60 years (including > 65 years and > 75 years) appear similar to those noticed in other large observational studies that compared SGLT2is versus DPP-4is in T2DM patients aged > 18 years [28–32]. They are also consistent with the results reported in large prospective placebo-controlled RCTs [5,6,33].

Data on the efficacy and safety of SGLT2is for old patients hospitalized for acute HF are rather scarce [34–36]. Nevertheless, all studies showed a good safety profile of SGLT2is. Only one analyzed the effects of hard clinical outcomes (significant reduction in combined risk of hHF or cardiac death) [34] while one focused on an improvement of symptoms [35] and another one on a reduction of biomarkers of HF [36] (see review in [10]).

Observational studies that compared older versus younger age groups

Several cohort studies carried out in different countries and populations compared CV endpoints in older versus younger patients with T2DM [13,16,17,23-27] (Table 2). In CVD-REAL Nordic, significant reductions with SGLT2is compared with other glucose-lowering agents were observed for both MACEs and CV mortality in patients aged ≥ 65 years whereas neutral associations were found in patients younger than 65 years [23]. Such interesting differences were also reported in two other studies that compared SGLT2i users versus DPP-4is users, one again from the CVD-REAL Nordic focusing on hHF plus CV mortality [25] and another one from the USA devoted to hHF [24] (Table 2). However, other studies did not find significant age-related interaction (p value > 0.05), whatever the criterion considered, when comparing outcomes of patients treated with SGLT2is versus sulphonylureas [26], DPP-4is [16,17,27] or liraglutide [17]. No obvious differences were noticed in studies that compared patients < 65 years vs. ≥ 65 years [23–26] and studies that compared patients < 75 years vs. ≥ 75 years [16,17]. The only exception issued from a study carried out in South Korea that compared SGLT2i users versus DPP-4i users [13]. Indeed, in contrast to previous studies, it reported less favourable results with SGLT2is regarding all-cause mortality, hHF and hHF combined with all-cause mortality in the subgroup of patients aged ≥ 75 years vs. the subgroup aged < 75 years (Table 2). The reason for such inconsistency is unclear.

Renal outcomes according to age

Only one third of T2DM patients with CKD eligible for SGLT2i is currently treated with SGLT2is in real-world clinical practice. The older patient group and clinical inertia are the main barriers to initiate SGLT2i for eligible patients [37]. As for CV outcomes, studies from the literature were analyzed in two different ways: first, studies that reported renal outcomes in patients with T2DM older than 60 years [14,20-22, 38-45] (Table 3), second studies that compared subgroups of different ages (Table 4). The composite renal outcome may vary across studies but most of them tested the decline of eGFR (for instance reduction by 40–50% from baseline) and the progression to ESRD. Overall, these minor differences did not impact the final conclusion.

Observational studies in T2DM patients older than 65 years

Studies were carried out in different countries worldwide. Very consistent results were reported with significant reductions in a composite renal outcome or progression to ESRD noticed with SGLT2is compared with oGLD [14,20,22,38-40], DPP-4is [41–43] and GLP-1RAs [21,44,45] (Table 3). Thus, these results in the elderly population with T2DM fully confirm those noticed in younger patients aged < 60 years in observational studies [46] as well as those previously reported in large prospective placebo-controlled RCTs summarized in several meta-analyses [8,47-49], an effect interestingly observed independently of the presence of diabetes [50]. Of note, a retrospective cohort study Canadian CKD population suggested that patients in real-life may be in worse condition compared to patients recruited in RCTs. T-Indeed, the British Columbia cohort experienced nearly double the outcomes of kidney failure, death from any cause, and doubling of serum creatinine than the placebo arms of RCTs CREDENCE and DAPA-CKD [51]. These differences in the baseline risk of the populations may suggest a greater absolute benefit provided by SGLT2is in real-life conditions than in patients recruited in RCTs, as previously discussed [10].

In contrast with what was initially frightened, the incidence of acute kidney injury (AKI) in diabetic patients was reduced with SGLT2is versus placebo in RCTs [52]. According to a meta-analysis of eight observational studies, we already reported that SGLT2i users experienced a reduced risk of AKI compared with non-users in real-life conditions (HR 0.61, 95% CI 0.55–0.67) [53]. A similar positive effect was also observed in older patients, notably in comparison with DPP-4i users (HR 0.71, 0.65–0.76) or GLP-1RA users (HR 0.81, 0.75–0.87) [54]. For instance, in a large US study that compared SGLT2is with GLP-1RAs, the risk of AKI was significantly reduced in patients with T2DM and a mean age of 72 years (HR 0.62; 0.55–0.71) [19]. Nevertheless, another study with a stratified analysis according to age showed that empagliflozin users versus linagliptin users experienced attenuated benefits with respect to AKI risk in the subgroup aged ≥ 65 years (adjusted HR, 0.70; 0.43–1.13) compared with patients < 65 years (adjusted HR 0.54; 0.36–0.79) [55].

Table 1
Comparison of cardiovascular outcomes with SGLT2is versus other glucose-lowering agents in elderly patients with type 2 diabetes in observational studies.

References	Country	SGLT2is (n)	Comparators (n)	Mean age (years)	Mean follow-up (months)	MACEs	hHF	All-cause mortality	CV mortality	All -cause mortality + HHF
Birkeland et al. 2017 [23]	Nordic	All 22,830	oGLD 68,490	61	11	0.78 (0.69–0.87)	0.70 (0.61–0.81)	0·51 (0.45–0.58)	0.53 (0.40–0.71)	NA
Heerspink et al. 2020 [14]	5 countries	All 35,561	oGLD 35,561	61	15	NA	0.60 (0.47–0.76)	0.55 (0.48–0.64)	NA	NA
Han et al. 2020 [13]	South Korea	All 15,699	DPP-4is 15,699	72	12	NA	0.86 (0.76–0.97)	0.85 (0.75–0.98)	NA	0.86 (0.78–0.94)
Fralick et al. 2021 [15]	Canada	All 29,916	DPP-4is 29,916	71	13	NA	0.43 (0.37–0.49)	NA	NA	0.49 (0.45–0.54)
Patorno et al. 2021 [19]	US	All 45,047	GLP-1RAs 45,047	71.5	6	0.98 (0.87–1.10)	0.68 (0.59–0.80)	0.95 (0.81–1.11)	0.83 (0.64–1.07)	NA
Schechter et al. 2021 [20]	Israel	All 9219	oGLD 9219	62.3	20	0.67 (0.57–0.80) (*)	0.77 (0.58–1.03)	0.57 (0.45–0.71)	NA	0.62 (0.51–0.75)
Nakai et al. 2022 [16]	Japan	All 872	DPP-4is 821	≥ 75	12	NA	0.59 (0.47–0.74)	0.68 (0.51–0.90)	NA	NA
Desai et al. 2022 [18]	US	Empagliflozin 11,429	Sitagliptin 11,429	72	6	NA	0.67 (0.48–0.92)	0.91 (0.67–1.24)	NA	NA
Desai et al. 2022 [18]	US	Empagliflozin 17,502	GLP-1RAs 17,502	72	6	NA	0.85 (0.63–1.13)	0.90 (0.71–1.14)	NA	NA
Htoo et al. 2022 [17]	US	Empagliflozin 22,812	Sitagliptin 22,812	72	5	0.68 (0.60–0.77)	0.45 (0.36–0.56)	0.64 (0.53–0.78)	NA	NA
Htoo et al. 2022 [17]	US	Empagliflozin 22,894	Liraglutide 22,894	72	5	0.90 (0.79–1.03)	0.66 (0.52–0.82)	0.97 (0.79–1.17)	NA	NA
Baviera et al. 2022 [21]	Italy	All 11,470	GLP-1RAs 12,062	66	34	1.14 (1.02–1.27)	0.90 (0.76–1.08)	1.12 (1.00–1.27)	NA	NA
Gonzalez Perez et al. 2023 [22]	UK	All 12,978	oGLD 44,286	60	27	0.75 (0.61–0.93)	NA	0.56 (0.49–0.63)	NA	NA

Results are expressed as hazard ratio with 95% confidence interval.
CV: cardiovascular. DPP-4is: dipeptidyl peptidase-4 inhibitors. GLP1RAs: glucagon-like peptide-1 receptor agonists. hHF: hospitalization for heart failure. MACEs: major cardiovascular adverse events. NA: not available. oGLD: other glucose-lowering drugs. SGLT2is: sodium-glucose cotransporter 2 inhibitors.
(*) All-cause mortality instead of cardiovascular mortality.

Table 2
Observational studies that compared cardiovascular effects of SGLT2is in different age subgroups.

References	Country	SGLT2is	Comparators	Age Category (years)	MACEs	hHF	All-cause mortality	CV mortality	MACE + Hhf	All-cause mortality + hHF
Birkeland et al. 2017 [23]	Nordic	All	oGLD	< 65	1.01 (0.85–1.20)	NA	NA	1.10 (0.65–1.84)	NA	NA
				≥ 65	0.66 (0.56–0.78)	NA	NA	0.45 (0.32–0.65)	NA	NA
					P interaction = NA			P interaction = NA		
Gautam et al. 2017 [24]	USA	All	DPP4-is	< 65	NA	0.77 (0.58–1.05)	NA	NA	NA	NA
				≥ 65	NA	0.60 (0.41–0.87)	NA	NA	NA	NA
						P interaction = NA				
Dawwas et al. 2019 [26]	USA	All	SUs	≤ 65	0.59 (0.52–0.66)	NA	NA	NA	NA	NA
				> 65	0.89 (0.65–1.00)	NA	NA	NA	NA	NA
					P interaction = 0.420					
Pasternak et al. 2019 [25]	Nordic	All	DPP-4is	< 65	NA	NA	NA	NA	1.13 (0.94–1.35)	NA
				≥ 65	NA	NA	NA	NA	0.81 (0.69–0.96)	NA
									P interaction = 0.01	
Han et al. 2020 [13]	South Korea	All	DPP-4is	< 75	NA	0.79 (0.66–0.93)	0.72 (0.58–0.89)	NA	NA	0.77 (0.67–0.88)
				≥ 75	NA	0.95 (0.79–1.14)	0.93 (0.77–1.11)	NA	NA	0.93 (0.81–1.06)
						P interaction < 0.001	P interaction < 0.001			P interaction < 0.001
Htoo et al. 2022 [17]	US	Empagliflozin	Sitagliptin	< 75	0.72 (0.61–0.85)	0.40 (0.30–0.54)	NA	NA	NA	NA
				≥ 75	0.63 (0.52–0.77)	0.46 (0.33–0.64)	NA	NA	NA	NA
					P interaction = 0.34	P interaction = 0.50				
Htoo et al. 2022 [17]	US	Empagliflozin	Liraglutide	<75	0.91 (0.77–1.07)	0.67 (0.50–0.91)	NA	NA	NA	NA
				≥ 75	0.96 (0.77–1.20)	0.70 (0.50–0.97)	NA	NA	NA	NA
					P interaction = 0.62	P interaction = 0.90				
Nakai et al. 2022 [16]	Japan	All	DPP-4is	< 65	NA	0.38 (0.27–0.54)	0.51 (0.25–0.84)	NA	NA	NA
				65–74	NA	0.48 (0.36–0.85)	0.79 (0.49–1.27)	NA	NA	NA
				≥ 75	NA	0.52 (0.45–0.61)	0.58 (0.61–0.90)	NA	NA	NA
						P interaction = 0.16	P interaction = 0.81			
Yang et al. 2022 [27]	Taiwan	All	DPP-4is	< 60	0.53 (0.43–0.66)	0.56 (0.45–0.70)	NA	NA	NA	NA
				≥ 60	0.66 (0.56–0.77)	0.52 (0.45–0.62)	NA	NA	NA	NA
					P interaction = NA	P interaction = NA				

Results are expressed as hazard ratio with 95% confidence interval.
CV: cardiovascular. DPP-4is: dipeptidyl peptidase-4 inhibitors. hHF: hospitalization for heart failure. MACEs: major cardiovascular adverse events. NA: not available. oGLD oral glucose-lowering drugs. SGLT2is: sodium-glucose cotransporter type 2 inhibitors. SUs: sulphonylureas.

Table 3
Comparison of kidney outcomes with SGLT2is versus other glucose-lowering agents in elderly patients in observational studies.

References	Country	Type of comparator	SGLT2is (n)	Comparators (n)	Mean age (Years)	Mean follow-up (Months)	Composite renal outcome	ESRD
Heerspink et al. 2020 [14]	5 countries	oGLD	35,561	35,561	61	15	0.49 (0.35–0.67)	0.33 (0.16–0.68)
Pasternak et al. 2020 [41]	Scandinavia	DPP-4is	29,887	29,887	61.3	20	0.42 (0.34–0.53)	0.32 (0.22–0.47)
Takeuchi et al. 2020 [38]	Japan	oGLD	1433	2739	61.0	17	0.70 (0.50–0.98)	NA
Nagasu et al. 2021 [40]	Japan	oGLD	1033	1033	64.4	24	0.40 (0.26–0.61)	0.26 (0.11–0.61)
Koh et al. 2021 [39]	Korea	oGLD	12,652	11,893	≥ 65	18	NA	0.67 (0.41–1.09)
Schechter et al. 2021 [20]	Israel	oGLD	9219	9219	62.3	20	0.70 (0.57–0.85)	0.61 (0.23–1.67)
Baviera et al. 2022 [21]	Italy	GLP-1RAs	11,470	12,062	66	34	0.33 (0.16–0.62)	NA
Lui et al. 2022 [44]	Hong Kong	GLP-1RAs	695	653	≥ 65	13	0.650 (0.443- 0.955)	NA
Park et al. 2022 [42]	Korea	DPP-4is	267	285	≥ 65	36	0.66 (0.37–1.18) (*)	NA
Au et al. 2022 [43]	Hong Kong	DPP-4is	6333	25,332	61.5	45	NA	0.51 (0.42–0.62)
Kobayashi et al. 2022 [45]	Japan	GLP-1RAs	134	134	64.5	36	0.59 (0.35–0.99)	NA
Gonzalez Perez et al. 2023 [22]	UK	oGLD	12,978	44,286	60	27	0.55 (0.46–0.67)	NA

Results are expressed as hazard ratio with 95% confidence interval. (*) Primary outcome: progression to eGFR < 45 ml/min/1.73 m^2.
DPP-4is: dipeptidyl peptidase-4 inhibitors. ESRD: end-stage renal disease. GLP-1RAs: glucagon-like peptide-1 receptor agonists. NA: not available. oGLD oral glucose-lowering drugs. SGLT2is: sodium-glucose cotransporter type 2 inhibitors.

Observational studies that compared older versus younger age groups

A few cohort studies carried out mainly in Asian countries compared renal endpoints in older versus younger aged patients with T2DM [39,40-42, 44] (Table 4). A significant reduction in composite renal outcome and ESRD was observed among SGLT2i users compared with non-users whatever the age category, without any significant interaction between the age subgroups. Of note, the cutoff was set at the age 65 years in all published studies. Thus, no specific information is available in the very old population (≥ 75 years) regarding this specific analysis.

Safety of SGLT2is in the elderly population

The purpose of this paper was to investigate the efficacy rather the safety when using SGLT2is in the elderly population with T2DM. As recently reviewed [10,56], SGLT2is are generally well-tolerated amongst old diabetic patients with a similar pattern of adverse events as that observed in younger patients [57]. Nevertheless, limited data exists regarding the risk of serious adverse events in very old (≥ 75 years) T2DM patients treated with SGLT2is [58] and routine monitoring is recommended, with a special focus on a risk of volume depletion [59–61]. The benefit–risk profile of SGLT2is in older frail adults has yet to be fully explored [62]. Pooled analyses of RCTs have demonstrated good tolerability of SGLT2is in adults aged ≥ 65 years and even ≥ 75 years, yet in more limited samples, with the different SGLT2is commercialized worldwide, canagliflozin [63,64], dapagliflozin [65], empagliflozin [66] and ertugliflozin [67]. These favourable results have been confirmed in several observational studies in real-life conditions, which is reassuring.

Conclusion

The benefits of SGLT2is on cardiovascular disease, heart failure and kidney function as observed in RCTs translate to patients treated in clinical practice with no evidence that the positive effects are modified by age. In addition to evidence of cardiorenal protection from RCTs, observational cohort studies have provided supportive data emphasizing the benefits and safety profile of SGLT2is among elderly diabetic patients in “real-life practice” when compared with other glucose-lowering drugs or incretin-based therapies. Because the background risk of heart failure and diabetic kidney disease is higher in older patients, the absolute benefit provided by SGLT2is may be greater in this aged group compared to younger patients. Of course, pharmacological therapy should be tailored to the individual patient characteristics, especially in elderly people, a population that may be very heterogeneous [59]. Older frail patients were less well investigated in both clinical trials and observational studies and should probably require more caution and regular monitoring.

Table 4
Observational studies that compared renal effects of SGLT2is in different age subgroups.

References	Country	Type of comparators	SGLT2is (n)	Comparators (n)	Age category (Years)	Composite renal outcome	P interaction	ESRD	P interaction
Pasternak et al. 2020 [41]	Scandinavia	DPP-4is	17,984	17,984	35–64	0.42 (0.30- 0.59)	$P = 0.985$	NA	NA
			11,903	11,903	65–85	0.43 (0.32–0.56)		NA	
Koh et al. 2021 [39]	Korea	oGLD	32,364	33,123	<65	NA	NA	0.35 (0.23–0.55)	$P = 0.06$
			12,652	11,893	≥ 65	NA		0.67 (0.41–1.09)	
Nagasu et al. 2021 [40]	Japan	oGLD	NA	N A	<65	0.35 (0.20–0.62)	$P = 0.58$	0.19 (0.05–0.65	$P = 0.58$
			NA	NA	≥ 65	0.45 (0.24–0.86)		0.36 (0.12–1.13)	
Lui et al. 2022 [44]	Hong Kong	GLP-1RAs	1856	1898	<65	0.821 (0.630- 1.071)	$P = 0.310$	NA	NA
			695	653	≥ 65	0.650 (0.443- 0.955)		NA	
Park et al. 2022 [42]	Korea	DPP-4is	931	913	<65	0.33 (0.16–0.69) (*)	$P = 0.142$	NA	NA
			267	285	≥ 65	0.66 (0.37–1.18)		NA	

Results are expressed as hazard ratio with 95% confidence interval. (*) Primary outcome: progression to eGFR < 45 ml/min/1.73 m^2.
DPP-4is: dipeptidyl peptidase-4 inhibitors. ESRD: end-stage renal disease. GLP1RAs: glucagon-like peptide-1 receptor agonists. NA: not available. oGLD oral glucose-lowering drugs. SGLT2is: sodium-glucose cotransporter type 2 inhibitors.

Disclosure

A.J. Scheen has received lecturer/scientific advisor/clinical investigator fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, NovoNordisk and Sanofi. He worked as clinical investigators in TECOS, LEADER, HARMONY OUTCOME, PIONEER 6, EMPA-REG OUTCOME, CANVAS-R and DECLARE-TIMI 58 cardiovascular outcome trials.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] ElSayed NA, Aleppo G, Aroda VR, et al. 10. Cardiovascular disease and risk management: standards of care in diabetes-2023. Diabetes Care 2023;46(Suppl 1):S158–S90.
[2] Kenny HC, Abel ED. Heart failure in type 2 diabetes mellitus. Circ Res 2019;124:121–41.
[3] Kidney Disease: Improving Global Outcomes Diabetes Work G. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2022;102(5S):S1–S127.
[4] Scheen AJ. Sodium-glucose co-transporter type 2 inhibitors for the treatment of type 2 diabetes mellitus. Nature Rev Endocrinol 2020;16:556–77.
[5] Giugliano D, Longo M, Scappaticcio L, et al. SGLT-2 inhibitors and cardiorenal outcomes in patients with or without type 2 diabetes: a meta-analysis of 11 CVOTs. Cardiovasc Diabetol 2021;20:236.
[6] Usman MS, Khan MS, Fonarow GC, et al. Robustness of outcomes in trials evaluating sodium-glucose co-transporter 2 inhibitors for heart failure. ESC Heart Fail 2022;9:885–93.
[7] Scheen AJ. Counteracting heart failure with diabetes drugs: a review into the pharmacokinetic and pharmacodynamic properties. Expert Opin Drug Metab Toxicol 2022;18:381–93.
[8] Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2019;7:845–54.
[9] Bailey CJ, Day C, Bellary S. Renal protection with SGLT2 inhibitors: effects in acute and chronic kidney disease. Curr Diab Rep 2022;22:39–52.
[10] Scheen AJ, Bonnet F. Efficacy and safety profile of SGLT2 inhibitors in the elderly: how is the benefit/risk balance? Diabetes Metab 2023;49:101419.
[11] Sridhar VS, Rahman HU, Cherney DZI. What have we learned about renal protection from the cardiovascular outcome trials and observational analyses with SGLT2 inhibitors? Diabetes Obes Metab 2020;22(Suppl 1):55–68.
[12] Fadini GP, Del Prato S, Avogaro A, et al. Challenges and opportunities in real-world evidence on the renal effects of sodium-glucose cotransporter-2 inhibitors. Diabetes Obes Metab 2022;24:177–86.
[13] Han SJ, Ha KH, Lee N, et al. Effectiveness and safety of sodium-glucose co-transporter-2 inhibitors compared with dipeptidyl peptidase-4 inhibitors in older adults with type 2 diabetes: a nationwide population-based study. Diabetes Obes Metab 2021;23:682–91.
[14] Heerspink HJL, Karasik A, Thuresson M, et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. Lancet Diabetes Endocrinol 2020;8:27–35.
[15] Fralick M, Colacci M, Thiruchelvam D, et al. Sodium-glucose co-transporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors and the risk of heart failure: a nationwide cohort study of older adults with diabetes mellitus. Diabetes Obes Metab 2021;23:950–60.
[16] Nakai M, Iwanaga Y, Kanaoka K, et al. Contemporary use of SGLT2 inhibitors in heart failure patients with diabetes mellitus: a comparison of DPP4 inhibitors in a nationwide electric health database of the superaged society. Cardiovasc Diabetol 2022;21:157.
[17] Htoo PT, Tesfaye H, Schneeweiss S, et al. Comparative effectiveness of empagliflozin vs liraglutide or sitagliptin in older adults with diverse patient characteristics. JAMA Netw Open 2022;5:e2237606.
[18] Desai RJ, Glynn RJ, Everett BM, et al. Comparative effectiveness of empagliflozin in reducing the burden of recurrent cardiovascular hospitalizations among older adults with diabetes in routine clinical care. Am Heart J 2022;254:203–15.
[19] Patorno E, Pawar A, Bessette LG, et al. Comparative effectiveness and safety of sodium-glucose cotransporter 2 inhibitors versus glucagon-like peptide 1 receptor agonists in older adults. Diabetes Care 2021;44:826–35.
[20] Schechter M, Melzer-Cohen C, Rozenberg A, et al. Cardiorenal outcomes with sodium/glucose cotransporter-2 inhibitors in patients with type 2 diabetes and low kidney risk: real world evidence. Cardiovasc Diabetol 2021;20:169.
[21] Baviera M, Foresta A, Colacioppo P, et al. Effectiveness and safety of GLP-1 receptor agonists versus SGLT-2 inhibitors in type 2 diabetes: an Italian cohort study. Cardiovasc Diabetol 2022;21:162.
[22] Gonzalez Perez A, Vizcaya D, Saez ME, et al. Cardiovascular and renal outcomes among patients with type 2 diabetes using SGLT2 inhibitors added to metformin: a population-based cohort study from the UK. BMJ Open Diabetes Res Care 2023;11:e003072.
[23] Birkeland KI, Jorgensen ME, Carstensen B, et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. Lancet Diabetes Endocrinol 2017;5:709–17.
[24] Gautam S, Agiro A, Barron J, et al. Heart failure hospitalization risk associated with use of two classes of oral antidiabetic medications: an observational, real-world analysis. Cardiovasc Diabetol 2017;16:93.
[25] Pasternak B, Ueda P, Eliasson B, et al. Use of sodium glucose cotransporter 2 inhibitors and risk of major cardiovascular events and heart failure: scandinavian register based cohort study. BMJ 2019;366:l4772.
[26] Dawwas GK, Smith SM, Park H. Cardiovascular outcomes of sodium glucose cotransporter-2 inhibitors in patients with type 2 diabetes. Diabetes Obes Metab 2019;21:28–36.
[27] Yang CT, Peng ZY, Chen YC, et al. Cardiovascular benefits with favorable renal, amputation and hypoglycemic outcomes of SGLT-2 inhibitors in type 2 diabetes from the Asian perspective: a population-based cohort study and systematic review. Front Endocrinol (Lausanne) 2022;13:836365.
[28] Seino Y, Kim DJ, Yabe D, et al. Cardiovascular and renal effectiveness of empagliflozin in routine care in East Asia: results from the EMPRISE East Asia study. Endocrinol Diabetes Metab 2021;4:e00183.
[29] Patorno E, Pawar A, Wexler DJ, et al. Effectiveness and safety of empagliflozin in routine care patients: results from the EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study. Diabetes Obes Metab 2022;24:442–54.
[30] Filion KB, Lix LM, Yu OH, et al. Sodium glucose cotransporter 2 inhibitors and risk of major adverse cardiovascular events: multi-database retrospective cohort study. BMJ 2020;370:m3342.
[31] Peng ZY, Yang CT, Kuo S, et al. Restricted mean survival time analysis to estimate SGLT2i-associated heterogeneous treatment effects on primary and secondary prevention of cardiorenal outcomes in patients with type 2 diabetes in Taiwan. JAMA Netw Open 2022;5:e2246928.
[32] Idris I, Zhang R, Mamza JB, et al. Lower risk of hospitalisation for heart failure, kidney disease and death with sodium glucose co-transporter-2 compared to dipeptidyl peptidase-4 inhibitors in type 2 diabetes regardless of prior cardiovascular or kidney disease: a retrospective cohort study in UK primary care. Diabetes Obes Metab 2021;23:2207–14.
[33] Giugliano D, Longo M, Maiorino MI, et al. Efficacy of SGLT-2 inhibitors in older adults with diabetes: systematic review with meta-analysis of cardiovascular outcome trials. Diabetes Res Clin Pract 2020;162:108114.
[34] Amioka M, Sanada R, Matsumura H, et al. Impact of SGLT2 inhibitors on old age patients with heart failure and chronic kidney disease. Int J Cardiol 2023;370:294–9.
[35] Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med 2022;28:568–74.
[36] Perez-Belmonte LM, Sanz-Canovas J, Millan-Gomez M, et al. Clinical benefits of empagliflozin in very old patients with type 2 diabetes hospitalized for acute heart failure. J Am Geriatr Soc 2022;70:862–71.
[37] Jeong SJ, Lee SE, Shin DH, et al. Barriers to initiating SGLT2 inhibitors in diabetic kidney disease: a real-world study. BMC Nephrol 2021;22:177.
[38] Takeuchi M, Ogura M, Minoura T, et al. Comparative effectiveness of sodium-glucose cotransporter-2 inhibitors versus other classes of glucose-lowering medications on renal outcome in type 2 diabetes. Mayo Clin Proc 2020;95:265–73.
[39] Koh ES, Han K, Nam YS, et al. Renal outcomes and all-cause death associated with sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL 3 Korea). Diabetes Obes Metab 2021;23:455–66.
[40] Nagasu H, Yano Y, Kanegae H, et al. Kidney outcomes associated with SGLT2 inhibitors versus other glucose-lowering drugs in real-world clinical practice: the Japan chronic kidney disease database. Diabetes Care 2021;44:2542–51.
[41] Pasternak B, Wintzell V, Melbye M, et al. Use of sodium-glucose co-transporter 2 inhibitors and risk of serious renal events: scandinavian cohort study. BMJ 2020;369:m1186.
[42] Park G, Choi B, Kang S, et al. Sodium-glucose cotransporter-2 inhibitors could help delay renal impairment in patients with type 2 diabetes: a real-world clinical setting. J Clin Med 2022;11:5259.
[43] Au PCM, Tan KCB, Cheung BMY, et al. Association between SGLT2 inhibitors vs DPP4 inhibitors and renal outcomes among patients with type 2 diabetes. J Clin Endocrinol Metab 2022;107:e2962–e70.
[44] Lui DTW, Au ICH, Tang EHM, et al. Kidney outcomes associated with sodium-glucose cotransporter 2 inhibitors versus glucagon-like peptide 1 receptor agonists: a real-world population-based analysis. EClinicalMedicine 2022;50:101510.
[45] Kobayashi K, Toyoda M, Hatori N, et al. Comparison of renal outcomes between sodium glucose co-transporter 2 inhibitors and glucagon-like peptide 1 receptor agonists. Diabetes Res Clin Pract 2022;185:109231.

[46] Deng Y, Ghamsari F, Lu A, et al. Use of real-world evidence data to evaluate the comparative effectiveness of second-line type 2 diabetes medications on chronic kidney disease. J Clin Transl Endocrinol 2022;30:100309.
[47] Zhang X, Zhong Z, Li Y, et al. Long-term renal outcomes associated with sodium glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Metab Res Rev 2020;36:e3303.
[48] Kaze AD, Zhuo M, Kim SC, et al. Association of SGLT2 inhibitors with cardiovascular, kidney, and safety outcomes among patients with diabetic kidney disease: a meta-analysis. Cardiovasc Diabetol 2022;21:47.
[49] Li N, Lv D, Zhu X, et al. Effects of SGLT2 inhibitors on renal outcomes in patients with chronic kidney disease: a meta-analysis. Front Med 2021;8:728089.
[50] Nuffield Department of Population Health Renal Studies G. Consortium SiM-AC-RT. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet 2022;400:1788–801.
[51] Yi TW, Atiquzzaman M, Zheng Y, et al. Findings of sodium-glucose cotransporter-2 inhibitor kidney outcome trials applied to a Canadian chronic kidney disease population: a retrospective cohort study. Can J Kidney Health Dis 2022;9:20543581221145068.
[52] Scheen AJ, Delanaye P. Acute renal injury events in diabetic patients treated with SGLT2 inhibitors: a comprehensive review with a special reference to RAAS blockers. Diabetes Metab 2022;48:101315.
[53] Delanaye P, Scheen AJ. Epidemiology of acute kidney injury adverse events with SGLT2 inhibitors: a meta-analysis of observational cohort studies. Diabetes Epidemiol Manag 2021;3:100021.
[54] Zhuo M, Paik JM, Wexler DJ, et al. SGLT2 inhibitors and the risk of acute kidney injury in older adults with type 2 diabetes. Am J Kidney Dis 2022;79:858–67 e1.
[55] Lee YT, Hsu CN, Fu CM, et al. Comparison of adverse kidney outcomes with empagliflozin and linagliptin use in patients with type 2 diabetic patients in a real-world setting. Front Pharmacol 2021;12:781379.
[56] Adams J, Mosler C. Safety and efficacy considerations amongst the elderly population in the updated treatment of heart failure: a review. Expert Rev Cardiovasc Ther 2022;20:529–41.
[57] Scheen AJ. An update on the safety of SGLT2 inhibitors. Expert Opin Drug Safety 2019;18:295–311.
[58] Inagaki N, Nangaku M, Sakata Y, et al. Real-world safety and effectiveness of canagliflozin treatment for type 2 diabetes mellitus in Japan: SAPPHIRE, a long-term, large-scale post-marketing surveillance. Adv Ther 2022;39:674–91.
[59] Scheen AJ. Careful use to minimize adverse events of oral antidiabetic medications in the elderly. Expert Opin Pharmacother 2021;22:2149–65.
[60] American Diabetes Association Professional Practice Committee, Draznin B, Aroda VR, et al. 13. Older adults: standards of medical care in diabetes-2022. Diabetes Care 2022;45(Suppl 1):S195–207.
[61] Pollack R, Cahn A. SGLT2 inhibitors and safety in older patients. Heart Fail Clin 2022;18:635–43.
[62] Scheen AJ. SGLT2 inhibitors: benefit/risk balance. Curr Diab Rep 2016;16:92.
[63] Sinclair A, Bode B, Harris S, et al. Efficacy and safety of canagliflozin compared with placebo in older patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. BMC Endocr Disord 2014;14:37.
[64] Sinclair AJ, Bode B, Harris S, et al. Efficacy and safety of canagliflozin in individuals aged 75 and older with type 2 diabetes mellitus: a pooled analysis. J Am Geriatr Soc 2016;64:543–52.
[65] Fioretto P, Mansfield TA, Ptaszynska A, et al. Long-term safety of dapagliflozin in older patients with type 2 diabetes mellitus: a pooled analysis of phase IIb/III studies. Drugs Aging 2016;33:511–22.
[66] Kohler S, Zeller C, Iliev H, et al. Safety and tolerability of empagliflozin in patients with type 2 diabetes: pooled analysis of phase I-III clinical trials. Adv Ther 2017;34:1707–26.
[67] Pratley R, Dagogo-Jack S, Charbonnel B, et al. Efficacy and safety of ertugliflozin in older patients with type 2 diabetes: a pooled analysis of phase III studies. Diabetes Obes Metab 2020;22:2276–86.