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Highlights

- Older patients with T2DM and heart failure represent an increasing population.
- SGLT2is reduce the risk of cardiovascular complications and heart failure.
- SGLT2is may be associated with adverse events, a concern in older patients.
- Both efficacy and safety findings are similar in older versus younger patients.
- The benefit/risk balance of SGLT2is is favorable in elderly patients.

Journal Pre-proof

Efficacy and safety profile of SGLT2 inhibitors in the elderly: how is the benefit/risk balance?

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Short title : SGLT2 inhibitors in elderly

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Summary

Type 2 diabetes mellitus (T2DM) is a highly prevalent health condition in the aging population. Older adults with T2DM have higher risks of cardiovascular disease, heart failure (long underestimated) and premature death than those without diabetes. SGLT2 inhibitors have proven their ability to improve cardiovascular prognosis and reduce the risk of hospitalization for heart failure (hHF). However, several adverse events have been reported, whose incidence and severity might be increased in the elderly population. The aims of this comprehensive review were to analyze the benefit-risk ratio of SGLT2i therapy in older patients with T2DM by collecting data from (i) large prospective placebo-controlled

cardiovascular outcome trials (including those dedicated to heart failure), using both original publications and dedicated post-hoc analyses across different age groups and (ii) observational cohort studies, describing the effects of SGLT2is versus other glucose-lowering agents on cardiovascular outcomes and hHF in elderly patients or these effects in different age groups. Overall, consistent results showed a similar relative risk reduction in cardiovascular mortality and hHF with SGLT2is independently of age. The absolute risk reduction may be greater in elderly because of a higher background risk in older versus younger patients. Similarly, the safety profile of SGLT2is appeared comparable in older versus younger patients. In conclusion, the benefit/risk balance favors the use of SGLT2is in older patients at risk of cardiovascular disease and/or heart failure. Caution may be required in very old frail patients, especially those exposed to an increased risk of volume depletion.

Key-words : Aging – Elderly – Heart failure – SGLT2 inhibitor – Type 2 diabetes

Introduction

The risk of heart failure (HF) is increasing with aging [1], especially in the population with type 2 diabetes mellitus (T2DM) [2, 3]. HF is one of the cardiovascular (CV) diseases that impacts the most the geriatric population and this complication currently represents a major health problem [4]. HF with preserved left ventricular ejection fraction (HFpEF), rather than HF with reduced left ventricular ejection fraction (HFrEF), is particularly prevalent in the elderly population, even more in presence of T2DM [2, 3].

Sodium-glucose cotransporter type 2 inhibitors (SGLT2is) have demonstrated a marked reduction in hospitalization for heart failure (hHF), alone or combined with CV mortality, in patients with T2DM at high CV risk and in patients with both HFrEF and HFpEF, independently of the presence of diabetes [5-7]. They are the only glucose-lowering agents that can markedly reduce the risk of hHF in patients with T2DM [8]. They are now considered as part of preventive and curative approach to HF in patients with T2DM, but also without diabetes [2, 9-11]. Thus, SGLT2is may potentially represent an interesting therapeutic approach in older patients with T2DM, especially in those with or at risk for HF. However, safety concerns classically attributed to SGLT2is might be more problematic for elderly people [12], especially orthostatic hypotension, dehydration with a risk of acute renal injury, lower-limb amputations and urinary infections [9].

The present comprehensive review analyzes the effects of SGLT2is on CV outcomes, with a special focus on hHF, in older patients compared with younger patients with T2DM. For the purpose of concision, specific renal outcomes with SGLT2is across age groups will not be detailed in the present work. We first collect data from large prospective placebo-controlled cardiovascular outcome trials (CVOTs), using both original publications and dedicated post-hoc analyses across age groups. Then, we report findings of observational cohort studies, first those that compared the effects of SGLT2is versus other glucose-lowering agents on CV outcomes and hHF in elderly patients, second those that compared different age groups, especially < 65 years versus ≥ 65 years and < 75 years versus ≥ 75 years. Finally, after considering the safety profile of SGLT2is in older patients, we conclude with a benefit/risk balance analysis of SGLT2is in the elderly population.

Efficacy according to age subgroups in placebo-controlled randomized trials

All large-scale prospective RCTs and CVOTs with SGLT2is provided subgroups analyses, including across age groups. As previously emphasized [13], subgroup analyses are important if there are potentially large differences between groups in the risk of a poor outcome with or without treatment, if there are practical questions about when to treat, or if there are doubts about benefit in specific groups, such as elderly people. However, ideally analyses must be predefined, carefully justified, and limited to a few clinically important questions [14]. Post-hoc observations should be treated with caution irrespective of their statistical significance [13]. With the limitations of interaction effect in mind [15], a detailed analysis of results across different age groups in published studies with SGLT2is is provided below.

1) Cardiovascular outcome trials in patients with T2DM

In EMPA-REG OUTCOME, the first CVOT reported with SGLT2is, empagliflozin compared with placebo significantly reduced the incidence in major CV adverse events (MACE-3 points: CV mortality, nonfatal myocardial infarction, nonfatal stroke) by 29% in patients aged ≥ 65 years but surprisingly not in patients aged < 65 years (P interaction = 0.01) [16]. However, such a difference between these two age groups was not confirmed in three subsequent CVOTs, CANVAS with canagliflozin [17], DECLARE-TIMI 58 with dapagliflozin [18] and VERTIS-CV with ertugliflozin [19] (Table I). A meta-analysis of EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 indicated that the effect of

SGLT2is was consistent across all age groups: the hazard ratio (HR) for MACEs was 0.83 (95% confidence interval 0.71;0.96) in people aged ≥ 65 years and 0.95 (0.86;1.05) in people aged < 65 years, with no statistical subgroup difference ($P = 0.15$) [20]. Similarly, these last three CVOTs did not report differences regarding another major CV outcome (combination of hHF and CV mortality) in patients with T2DM aged ≥ 65 years versus < 65 years (Table I).

A similar effect independent of age was also reported in dedicated post-hoc secondary analyses that specifically compared the impact of SGLT2is on MACE-3 points and on hHF plus CV mortality composite outcome in patients with T2DM < 65 years, 65- < 75 years and ≥ 75 years in three CVOTs, EMPA-REG OUTCOME [21], CANVAS [22, 23] and DECLARE-TIMI 58 [24]. No significant difference was also found regarding the relative reduction of incident hHF across all age groups (Table II).

In an interesting post-hoc analysis of EMPA-REG OUTCOME, estimated mean survival was longer with empagliflozin than placebo at all ages. However, whereas the relative increases were consistent regardless of age and ranged between 12% and 15%, the absolute increases in mean survival with empagliflozin versus placebo decreased with age, from 4.5 years at the age of 45 down to 1.0 year at the age of 80 [25]. This finding is presumably explained by the natural diminution of life expectancy with age rather than by a reduction in efficacy of the pharmacological therapy with SGLT2i.

2) Renal outcome trials in patients with T2DM

Some data of interest may also be found in renal outcome trials with SGLT2is. In CREDENCE carried out in patients with T2DM and chronic kidney disease (CKD) [26], no significant difference was observed in the reduction of hHF plus CV mortality with canagliflozin versus placebo in individuals < 65 years (HR 0.64, 0.48;0.86) versus individuals ≥ 65 years (HR 0.73, 0.57;0.94), P interaction 0.509 [27]. Similar results were reported in SCORED for sotagliflozin in patients with diabetes and CKD: HR 0.60, 0.43;0.83 versus 0.79, 0.66;0.95 in patients < 65 years vs. ≥ 65 years, respectively [28]. No such analyses according to age have been published yet in the two more recent renal outcome trials, DAPA-CKD [29] and EMPA-KIDNEY [30].

3) Outcome trials in patients with HF (with or without T2DM)

Five CVOTs recruited patients with HF, two (with or without T2DM) with HFrEF (DAPA-HF, EMPEROR-Reduced) [31, 32] and two (with or without T2DM) with HFpEF

(EMPEROR-Preserved and DELIVER) [33, 34] and one with both types of HF in patients with T2DM (SOLOIST-Whf) [35]. In subgroup analyses that compared older versus younger patients, all trials investigated the effects of a SGLT2i versus placebo on the combination of hHF and CV mortality used as a primary endpoint. The cut-off was set at 65 years except in the two studies that recruited patients with HFpEF that used higher thresholds, 70 years [33] and 72 years [34], respectively. The favorable effects of SGLT2is were shown almost similar (no *P* for interaction provided) in older people compared with younger people, whatever the SGLT2i used (dapagliflozin, empagliflozin, sotagliflozin) and the type of HF (Table III).

Interestingly, the four studies devoted to HF_rEF and HF_pEF with either dapagliflozin or empagliflozin were analyzed in further publications specifically devoted to the influence of age on the effect of SGLT2is on the composite outcome hHF plus CV mortality [36-39]. Different age cut-offs were used across the four studies ranging from < 55 years to ≥ 80 years (Table IV). All studies gave consistent results with no significant interaction regarding the different age subgroups.

A meta-analysis of the DAPA-HF and EMPEROR-Reduced trials revealed that treatment with SGLT2is was associated with a significant 25% reduction in the combined risk of CV death and first hHF in patients with HF_rEF aged ≥ 65 years, independently of the presence of T2DM (HR 0.75, 0.66;0.85). Furthermore, this significant risk reduction remained consistent also among 2148 patients older than 75 years [40].

In another meta-analysis of four trials, SGLT2is reduced hHF (HR 0.62, 0.51-0.76) in patients ≥ 65 years, an effect that was not evident in patients < 65 years (HR 0.87, 0.63;1.07). However, the reduction in the composite endpoint hHF plus CV mortality was almost the same in both age groups: HR 0.78 (0.66;0.93) versus 0.79 (0.69;0.91), in patients ≥ 65 years vs. < 65 years [41]. When analyzing data of two trials that gave detailed results in patients ≥ 75 years versus < 75 years, the protection against hHF [HR 0.64 (0.36;1.12) versus 0.72 (0.61;0.84), *P* interaction 0.70] and hHF plus CV mortality [HR 0.71 (0.40;1.27) versus 0.76 (0.63;0.91), *P* interaction 0.83] were almost similar in both age groups ≥ 65 years versus < 65 years [41]. The same paper reported a similar analysis for glucagon-like peptide-1 receptor agonists (GLP-1RAs), which reduced MACE-3 points and its components but not hHF, independently of age [41].

In a larger meta-analysis of 10 clinical trials mentioned above (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI-68, VERTIS CV, CREDENCE, DAPA-CKD,

DAPA-HF; EMPEROR-Reduced, SCORED, SOLOIST), participants were divided into two subgroups, < 65 years and \geq 65 years. Both age groups favored SGLT2i use, with an almost equivalent significant reduction in the primary outcome combining hHF and CV mortality: < 65 years (629 events in 9,057 patients, 6.94%); odds ratio 0.79 (0.70;0.88), $P < 0.001$ versus placebo; \geq 65 years (970 events in 9,260 patients, 10.47%); odds ratio 0.78 (0.71;0.86), $P < 0.001$ versus placebo. Of note, heterogeneity was at 0% in all subgroups [42].

Efficacy of SGLT2is according to age in real-life observational studies

When examining medical records of all patients who had a diagnosis of HF from a medical center in the US, compared to randomized controlled trial (RCT) participants, eligible real-world patients were significantly older (mean age around 80 years) with worse renal function and more atrial fibrillation, and less T2DM [43]. Of note, SGLT2is were associated with a significant reduction in atrial fibrillation/flutter, a frequent complication in older patients with T2DM and/or HF [44]. Examining real-life data besides RCTs is of major interest, in particular because the comparator is another glucose-lowering agent instead of a placebo.

International literature provides two types of observational studies of potential interest: first, cohort studies carried out in elderly people (\geq 65 years) that compared CV outcomes in patients treated with SGLT2is versus those treated with another glucose-lowering agent [45-50] (Table V); second, cohort studies that compared CV outcomes in SGLT2i users versus non-users aged \geq 65 years versus < 65 years (Table S1; see supplementary materials associated with this article on line).

Observational studies in T2DM patients older than 65 years

Studies were performed in different countries (US, Canada, Scandinavia, Japan, South Korea) and SGLT2is were compared with different glucose-lowering agents: all types, dipeptidyl peptidase-4 inhibitors (DPP-4is), GLP-1 RAs [45-50] (Table V). Most studies used a propensity score matching to minimize potential biases. 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 or hHF combined with CV mortality reported significant lower incidence rates with SGLT2is compared with DPP-4is [45-49]. Results that compared SGLT2is with GLP-1 RAs were less consistent [48-50].

Overall, these results obtained in cohort patients aged > 65 years appear similar to those noticed in other large observational studies that compared SGLT2is versus DPP-4is in T2DM patients aged > 18 years [51-54]. They are also consistent with the results reported in large prospective placebo-controlled RCTs [6, 7].

Data on the efficacy and safety of SGLT2is for old patients hospitalized for acute HF are rather scarce. In a multinational RCT in patients hospitalized for acute HF (mean age 71 years), initiation of empagliflozin was well tolerated and compared with placebo resulted in significant clinical benefit (assessed by the Kansas City Cardiomyopathy Questionnaire Total Symptom Score) in the 90 days after starting treatment [55]. The OSHO-heart (Optimal Solution after Hospitalization in Onomichi for heart failure, Japan) was a prospective study of 213 patients aged ≥ 75 years hospitalized for acute decompensated HF with stage 3 to 4 CKD. In this study, it was found that SGLT2i therapy might reduce the combined risk of hHF or cardiac death and preserve a worsening renal function in old age patients with HF and CKD [56]. In a real-world observational study from Spain in very old (≥ 80 years) patients with T2DM hospitalized for acute HF, continuing preadmission empagliflozin reduced NT-proBNP (N-terminal pro-brain natriuretic peptide) levels and increased diuretic response and urine output, with a good safety profile. However, this study did not investigate harder clinical CV outcomes [57].

Observational studies in T2DM patients that compared older versus younger age

Several cohort studies carried out in different countries and populations compared CV endpoints in older versus younger aged patients with T2DM. 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 [58]. Such interesting differences were also reported in two other studies that compared SGLT2i users versus DPP-4is users, once again from the CVD-REAL Nordic focusing on hHF plus CV mortality [59] and another one from the USA devoted to hHF [60] (Table S1; see supplementary materials associated with this article on line). However, other studies did not find significant interaction (P value > 0.05), whatever the criterion considered, when comparing outcomes of patients treated with SGLT2is versus sulphonylureas [61], DPP-4is [47, 48] or liraglutide [48]. No obvious differences were noticed in studies that compared patients < 65 years versus ≥ 65 years [58-61] and studies that compared patients < 75 years versus ≥ 75 years [47, 48]. The only exception issued from a study carried out in South Korea that compared SGLT2i users versus

DPP-4is users [45]. Indeed, in contrast to previous studies, it reported less favorable results with SGLT2is regarding all-cause mortality, hHF and hHF combined with all-cause mortality in the subgroup of patients aged ≥ 75 years versus the subgroup aged < 75 years (Table S1; see supplementary materials associated with this article on line). The reason for such inconsistency is unclear.

Safety concerns with SGLT2is in elderly patients

The tolerance and safety profile of canagliflozin [62, 63], dapagliflozin [64], empagliflozin [65, 66] and ertugliflozin [67] has been investigated in subgroups of older patients with T2DM using pooled analyses of phase II-III RCTs. The incidences of all adverse events, serious adverse events, discontinuations and deaths in participants aged ≥ 65 years and those aged < 65 years were generally similar across the treatment groups with SGLT2is versus comparators (placebo or other glucose-lowering agents). Incidences of urinary tract infections, renal-related adverse events, adverse events related to volume depletion, and documented hypoglycemia episodes were similar across all treatment groups (canagliflozin versus comparator) in patients ≥ 65 years of age [62]. However, a higher incidence of adverse events related to volume depletion was observed with canagliflozin in very old people: the incidence of volume depletion-related adverse events with canagliflozin 100 and 300 mg versus placebo was 4.9% and 8.7% versus 2.6% in patients aged ≥ 75 years compared with 2.2% and 3.1% versus 1.4% in patients < 75 years. Of note, the proportion of participants taking background loop diuretics was numerically higher in individuals ≥ 75 years across treatment groups [63]. A similar observation was reported with dapagliflozin. Volume reduction adverse events were uncommon, but increased with age, with a slightly higher frequency with dapagliflozin 10 mg vs. placebo across all subgroups (< 65 years: 1.7 versus 1.2 %; ≥ 65 years: 2.3 versus 1.7 %; ≥ 75 years: 3.1 versus 2.6 %, respectively) [64]. The incidence of adverse events consistent with volume depletion was also higher with empagliflozin 10 mg and 25 mg versus placebo in participants aged ≥ 75 years but remained rather rare (3.2 and 3.0 versus 2.3/100 patient-years, respectively) [65]. However, according to a more recent pooled analysis of RCTs with empagliflozin, the frequency of events consistent with volume depletion was similar between patients treated with empagliflozin 10/25 mg and placebo in all subgroups, including patients ≥ 75 years [66]. In patients aged ≥ 65 years the incidence of volume depletion adverse events (including hypotension) was

slightly higher among ertugliflozin users than non-users (2.2% with 5 mg, 3.3% with 15 mg, compared to 1.3 % with placebo), an increase not observed in patients < 65 years [67].

After the report of a higher risk of lower-limb amputations with canagliflozin compared with placebo in the CANVAS trial (HR 1.97, 1.41;2.75), some anticipated risk factors for amputation were identified, but no at-risk subgroup for canagliflozin could be found. Especially, old age showed only a non-significant trend for a higher risk of lower-limb amputations: ≥ 65 years: HR 2.48 (1.39;4.43) versus < 65 years: HR 1.74 (1.16;2.63), *P* interaction 0.37 [68]. In a cohort study using three US nationwide databases, the increase in rate of amputation with canagliflozin was small and most apparent for adults aged ≥ 65 years with baseline CV disease (HR 1.73, 1.30;2.29). No significant increase was noticed in patients ≥ 65 years without CV disease (HR 1.30, 0.52;3.26) and only a marginal increase was observed in patients < 65 years [69]. In an observational study from Sweden and Denmark that reported an increased risk of lower-limb amputation with SGLT2is in comparison with GLP-1RAs, the risk was not exacerbated with increasing age: ≥ 65 years: HR 1.96 (0.96;4.00) versus 35- < 65 years: HR 2.88 (1.32;6.31) [70]. As a possible explanation for such an increased risk, independent of age, one might hypothesize a possible reduction in the risk of lower-limb amputations with GLP-1RAs rather than an increase with SGLT2is [71].

Dapagliflozin did not increase the risk of urinary tract infections, bone fractures or falls, regardless of age. Older dapagliflozin-treated patients had more renal adverse events than placebo-treated patients, the majority of which being non-serious small transient changes in serum creatinine [64]. A study examined the association of hospitalization for acute kidney injury (AKI) prior initiation of an SGLT2i compared with initiation of an incretin-based medication among older (mean age 72 years) adults with T2DM in routine practice; the risk of AKI was lower in the SGLT2i group than in the DPP-4i (HR 0.71, 0.65;0.76) or the GLP-1RA (HR 0.81, 0.75;0.87) group [72]. These findings are reassuring given a possible risk of SGLT2i -induced volume depletion and confirm those reported in the overall population with T2DM treated with SGLT2is irrespective of age [73].

In the Italian SOLD study, discontinuations of SGLT2i therapy because of adverse events were almost two times higher in patients aged ≥ 80 years, compared to younger patients (35% versus 19%, *P* = 0.005). Adverse events leading to discontinuation were genitourinary infections in 33% and intolerance (excessive diuresis, nausea, loss of appetite, ...) in 19% whereas symptoms of volume depletion (5.5%) and acute kidney injury (2.7%) were

rarely reported [74]. In a sub-analysis of data from the SGLT2i and Angiotensin receptor blocker Combination theRapy in pAtients with diabetes and uncontrolled nocturnal hypertension (SACRA) study in Japan, the incidences of hypoglycemic episodes, hypotension, and metabolic adverse events were similar in patients aged ≥ 75 years versus < 75 years [75]. In the SAPPHIRE study, a long-term post-marketing surveillance of canagliflozin in Japan, efficacy and safety data were analyzed across different age subgroups (< 65 , $\geq 65 - < 75$, and ≥ 75 years old). The most common type of adverse drug reactions was that related to volume depletion (body fluid decrease: 1.39%), almost at the same level as genital infections. Adverse drug reactions tended to increase with age (all adverse events from 9.60% to 14.41%; serious adverse events from 1.33% to 4.12% when comparing patients < 65 years and ≥ 75 years) and thus to be more common in very elderly patients [76].

In conclusion, SGLT2is are generally well-tolerated amongst the elderly population [4]. Nevertheless, limited data exists regarding the risk of serious adverse events in very old (≥ 75 years) T2DM patients treated with SGLT2i and routine monitoring is recommended, with a special focus on a risk of volume depletion, especially when (loop) diuretics are present [77, 78]. It is generally not recommended to monitor serum creatinine and kalemia after the initiation of SGLT2i therapy, including in older patients, yet more caution may be required in patients with advanced CKD [12, 79].

Benefit-Risk balance in elderly people

RCTs, designed for ascertaining the efficacy and the safety of SGLT2i therapy, were not tailored to elderly cohorts, so that the proportion of patients aged ≥ 75 years was rather limited [62-65, 67]. Considering the high prevalence of comorbidities and the elevated risk of drug-related side-effects in older patients, attention should be focused on the net risk-benefit ratio of SGLT2i prescription in these patients [77, 80, 81]. The benefit–risk profile of SGLT2is in older frail adults has yet to be fully explored [82], but pooled analyses have demonstrated good tolerability of SGLT2is in adults aged ≥ 65 years and even ≥ 75 years, yet in more limited samples [62-65, 67]. These results have been confirmed in several observational studies in real-life conditions worldwide, which is reassuring.

When compared with the safety profile of DPP-4is, that of SGLT2is raised more concerns, with the reports of some adverse events that may be more frequent and more severe in older patients, especially those characterized by frailty [79, 83]. However, and in contrast

with DPP-4is [84], SGLT2is have demonstrated CV protection, mainly a reduced risk of HF (\pm CV mortality) in patients with T2DM at high CV risk, with similar positive effects across age subgroups, including patients ≥ 65 years and ≥ 75 years (Tables I-IV). In patients with T2DM at high CV risk, the benefit-risk balance appears favorable [82], including in elderly patients. Overall, similar safety profiles have been reported for elderly and younger patients [81]. Nevertheless, more caution should most probably be recommended, especially if frailty is present. Age does not fully account for differences in older adults with diabetes [85], and frailty assessments may be more important than chronological age alone [86, 87]. In a post-hoc analysis of DAPA-HF [88], dapagliflozin improved all CV outcomes examined, regardless of frailty status. However, the absolute reductions were larger in more frail patients [88]. Similarly, in a post-hoc analysis of DELIVER, the benefit of dapagliflozin on the primary endpoint (hHF plus CV mortality) was consistent across the range of frailty studied. Nevertheless, the improvement in health-related quality of life with dapagliflozin occurred early and was greater in patients with a higher level of frailty [89].

Overall, the relative risk reduction in CV outcomes with SGLT2is is almost the same in older patients with T2DM compared with younger patients. However, as the absolute risk of CV complications, especially CV mortality and HF, is higher in older versus younger people, the absolute risk reduction provided by SGLT2is may be greater in elderly individuals at high risk, leading to a lower number-needed-to-treat (NNT) to avoid a severe CV complication [90]. Using data from the EMPA-REG OUTCOME trial, it has been estimated that empagliflozin improved survival by 1 to 4.5 years in patients with T2DM and established CV disease, a benefit regarding life expectancy still observed in patients > 70 years [25].

Of note, besides CV risk, patients with T2DM are exposed to a higher risk of CKD that may progress to end-stage renal disease, a complication not discussed in the present comprehensive review that is focusing on CV outcomes and HF [for recent update, see [91]]. The risk is even more important in older patients with long-standing T2DM. SGLT2is have proven nephroprotective effects and their ability to reduce albuminuria and the decline of glomerular filtration rate and ultimately the progression to end-stage renal disease requiring dialysis or transplantation [92, 93]. In the three renal outcome trials, the primary composite outcome (composite of progression of renal disease or death from renal or CV cause) was reduced with SGLT2is versus placebo in older patients, without significant difference when compared to younger patients: CREDENCE ≥ 65 years: HR 0.77 (0.60;1.00) [26], DAPA-CKD ≥ 65 years: HR 0.58 (0.43;0.77) [29], EMPA-KIDNEY ≥ 70 years: HR 0.65 (0.52;0.81)

[30]. Obviously, this renal benefit represents a major added value for SGLT2i therapy, also in the elderly population with or at risk of CKD.

Even if the effects of SGLT2is on stroke remain controversial [94], another unsuspected benefit of these glucose-lowering agents in older patients may result from a potential neuroprotective effect [95, 96]. Diabetes conferred a 1.25- to 1.91-fold excess risk for cognitive disorders (cognitive impairment and dementia) [97]. Cognitive dysfunction is common in elderly patients with T2DM and this disorder should be looked for and integrated in practical guidelines [77]. The knowledge of connections between T2DM and cognitive dysfunction is increasing [98], which should search for effective management of both comorbidities [99]. Potential mechanisms of SGLT2is in conditions connected with neuronal damage, with special emphasis on Alzheimer's disease and cerebral ischemia, have been reviewed in preclinical studies [95, 100], a positive effect that may also be present in patients with T2DM, [101, 102]. Some nested case-control studies and population-based retrospective cohort studies revealed an association between SGLT2i use and improved cognitive scores globally and in language domain and executive function [103] and a lower risk of dementia [104-106]. Significant beneficial effects of empagliflozin were also reported on cognitive and physical impairment in frail older adults with diabetes and HFpEF [107]. Further studies should confirm that SGLT2is have a potential to protect against atherosclerosis, cognitive impairment, and dementia in older patients with T2DM. Further studies should be conducted and specifically powered to detect neurological outcomes in SGLT2i-treated older patients [96].

Additional trials that are focusing on elderly patients with T2DM are ongoing. However, they are of smaller size and not targeting CV outcomes. The Japanese EMPA-ELDERLY trial is the first randomized clinical trial of an SGLT2i in elderly patients with T2DM to evaluate effects on skeletal muscle mass, muscle strength and physical performance concurrently as well as changes in patient-reported outcomes (including quality of life), cognitive function and safety [108]. GOLDEN-AGE (Gliflozin in eLderly Diabetic patiENTs) is a pragmatic intraclass evaluation trial carried out in Italy that will compare both efficacy and safety of three commercially available SGLT2is (canagliflozin, dapagliflozin and empagliflozin) in a population of frail patients at high risk of CV and renal diseases (ClinicalTrials.gov Identifier: NCT04796428).

It is important to notice that elderly patients, in particular the very elderly, are not sufficiently represented not only in RCTs but also in available observational cohort studies. Thus, the management of elderly diabetic patients, including those with HF, should be mainly based on the integration of scientific evidence with appropriate clinical judgment and integration of individual patients' profiles [9]. Individualization of glycemic management in older people with T2DM is advised, especially because of the heterogeneity of the elderly population [77]. Of note, clinical practice recommendations may somewhat vary across countries in the different published guidelines [109].

Conclusion

Considering the recently updated international guidelines for the management of T2DM and HF, it is anticipated that SGLT2is will be more widely prescribed. Owing to the increase prevalence of both T2DM and HF in older people, the use of SGLT2is in this population will be increasingly common in clinical practice so that the benefit/risk balance certainly deserves attention. Stratified analyses of RCTs and CVOTs indicated that older patients have similar or even greater relative risk reductions in CV complications such as CV mortality and hHF compared with younger patients. These findings were confirmed in several observational studies worldwide. Of note, because the background risk of CV complications and hHF is higher in older patients, the absolute benefit provided by SGLT2is may be greater in this aged group compared to younger patients. Furthermore, besides CV benefits, SGLT2is could also exert positive effects on the progression of CKD and cognitive dysfunction, two complications frequently observed in the elderly population.

SGLT2i-associated side effects such as volume depletion, lower-limb amputations, urinary tract infections and worsening urinary incontinence may be more common in the elderly population. However, overall reassuring data were reported with a similar safety profile in older and younger patients, both in RCTs/CVOTs and in observational studies. Adverse events related to volume depletion are slightly increased with SGLT2is in older patients, yet their incidence remains rather low. Quality of life does not appear to be altered by SGLT2is in older patients and may be improved in patients with HF. Even if older frail patients should probably require more caution and regular monitoring, overall, the benefit/risk balance of using SGLT2is in older patients is highly favorable, especially in those at risk of CV disease and HF.

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.

F. Bonnet has received lecturer/scientific advisor fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, NovoNordisk and Sanofi.

Appendix supplementary material

Supplementary materials (Table S1) associated with this article can be found at <http://www.sciencedirect.com> at doi . . .

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Journal Pre-proof

Table I. Influence of age on the effects of SGLT2is in cardiovascular or renal placebo-controlled outcome trials:

data reported in original publications.

| Clinical trial | SGLT2 inhibitor | MACE-3 points | | | hHF + CV mortality | | |
|---------------------------|-----------------|---------------------|---------------------|----------------------|---------------------|---------------------|----------------------|
| | | < 65 years | ≥ 65 years | <i>P</i> interaction | < 65 years | ≥ 65 years | <i>P</i> interaction |
| EMPA-REG OUTCOME [16, 21] | Empagliflozin | 1.04 (0.84;1.29) | 0.71 (0.58;0.86) | 0.01 | 0.79 (0.60;1.05) | 0.58 (0.45;0.73) | NA |
| CANVAS [17, 22] | Canagliflozin | 0.91 (0.76;1.10) | 0.80 (0.67;0.95) | 0.26 | 0.65 (0.51;0.83) | 0.87 (0.71;1.07) | 0.09 |
| DECLAR E-TIMI 58 [18] | Dapagliflozin | 0.94 (0.82;1.08) | 0.93 (0.81;1.07) | 0.99 | 0.85 (0.69;1.04) | 0.79 (0.66;0.94) | 0.50 |
| VERTIS-CV [19] | Ertugliflozin | 0.90 (0.73;1.10) | 1.03 (0.86;1.22) | NS | 0.86 (0.66;1.11) | 0.89 (0.74;1.09) | NS |

Results are represented by hazard ratio (95 % confidence interval).

CV: cardiovascular. hHF: hospitalization for heart failure. MACEs: major cardiovascular adverse events. NA: not available. NS: not significant. SGLT2: sodium-glucose cotransporter type 2.

Table II. Influence of age on the effects of SGLT2is in cardiovascular or renal placebo-controlled outcome trials:

data reported in secondary analyses dedicated to age subgroups.

| Clinical trials | SGLT2 inhibitor | Outcomes | < 65 years | 65 -<75 years | ≥ 75 years | <i>P</i> interaction |
|-----------------------|-----------------|--------------------|---------------------|---------------------|---------------------|----------------------|
| EMPA-REG OUTCOME [21] | Empagliflozin | MACEs | 1.04 (0.84;1.29) | 0.74 (0.58;0.93) | 0.68 (0.46;1.00) | 0.047 |
| | | hHF + CV mortality | 0.78 (0.59;1.03) | 0.59 (0.44;0.80) | 0.52 (0.33;0.82) | 0.240 |
| | | hHF | 0.73 (0.48;1.10) | 0.66 (0.44;1.00) | 0.45 (0.22;0.89) | 0.488 |
| CANVAS [22] | Canagliflozin | MACEs | 0.91 (0.76;1.10) | 0.80 (0.67;0.95) | | 0.26 |
| | | hHF + CV mortality | 0.65 (0.51;0.83) | 0.87 (0.71;1.07) | | 0.09 |
| | | hHF | NA | NA | | NA |
| DECLARE-TIMI 58 [24] | Dapagliflozin | MACEs | 0.93 (0.81;1.08) | 0.97 (0.83;1.13) | 0.84 (0.61;1.15) | 0.7352 |
| | | hHF + CV mortality | 0.88 (0.72;1.07) | 0.77 (0.63;0.94) | 0.94 (0.65;1.36) | 0.527 |
| | | hHF | 0.88 (0.68;1.15) | 0.60 (0.40;0.79) | 0.81 (0.50;1.30) | 0.1402 |

Results are represented by hazard ratio (95 % confidence interval).

CV: cardiovascular. hHF: hospitalization for heart failure. MACEs: major cardiovascular adverse events. SGLT2: sodium-glucose cotransporter type 2.

Table III. Influence of age on the effects of SGLT2is on cardiovascular outcomes in patients with heart failure: data reported in original publications.

| Clinical trials | SGLT2 inhibitor | Hospitalization for heart failure + cardiovascular mortality | |
|------------------------|-----------------|--|------------------|
| | | < 65 years | ≥ 65 years |
| DAPA-HF [31] | Dapagliflozin | 0.78 (0.63;0.96) | 0.72 (0.60;0.85) |
| EMPEROR-Reduced [32] | Empagliflozin | 0.71 (0.57;0.89) | 0.78 (0.66;0.93) |
| EMPEROR-Preserved [33] | Empagliflozin | 0.88 (0.70;1.11) | 0.75 (0.64;0.87) |
| DELIVER [34] | Dapagliflozin | 0.82 (0.69;0.97) | 0.81 (0.69;0.96) |
| SOLOIST-Whf [35] | Sotagliflozin | 0.79 (0.51;1.23) | 0.62 (0.47;0.82) |

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Table IV. Influence of age on the effects of SGLT2is on cardiovascular outcomes in patients with heart failure: data reported in dedicated secondary analyses.

| Clinical trials | SGLT2 inhibitor | Hospitalization for heart failure + cardiovascular mortality | | | | | |
|------------------------|-----------------|--|---------------------|---------------------|---------------------|---------------------|----------------------|
| | | <55 years | < 65 years | 65 ;<75 years | ≥ 75 years | ≥ 80 years | <i>P</i> interaction |
| DAPA-HF [36] | Dapagliflozin | 0.87 (0.60;1.28) | 0.71 (0.55;0.93) | 0.76 (0.61;0.95) | 0.68 (0.53;0.88) | | 0.76 |
| EMPEROR-Reduced [37] | Empagliflozin | 0.71 (0.57;0.89) | | 0.72 (0.57;0.93) | 0.86 (0.67;1.10) | | 0.25 |
| EMPEROR-Preserved [38] | Empagliflozin | 0.73 (0.57;0.95) | | 0.72 (0.55;0.95) | 0.86 (0.69;1.07) | 0.83 (0.61;1.14) | 0.33 |
| DELIVER [39] | Dapagliflozin | 0.80 (0.47;1.37) | 0.88 (0.65;1.19) | 0.79 (0.65;0.96) | 0.82 (0.69;0.98) | | 0.95 |

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

| References | Country | SGLT2i (n) | Comparator (n) | Age (Years) | Follow-up Months | MAC E-3 points | All-cause mortality + HHF | All-cause mortality | CV mortality | hHF |
|-----------------------------|-------------|--------------------------|--------------------------|-------------|------------------|-------------------|---------------------------|---------------------|-------------------|-------------------|
| Birkel and et al. 2017 [58] | Nordic | All (\approx 38054/2) | All (\approx 38054/2) | >65 | 11 | 0.66 (0.56; 0.78) | NA | NA | 0.45 (0.32; 0.65) | NA |
| Han et al. 2020 [45] | South Korea | All 15699 | DPP-4is 15699 | 72 | 12 | NA | 0.86 (0.78; 0.94) | 0.85 (0.75; 0.98) | NA | 0.86 (0.76; 0.97) |
| Fralick et al. 2021 [46] | Canada | All 29916 | DPP-4is 29916 | 71 | 13 | NA | 0.49 (0.45; 0.54) | NA | NA | 0.43 (0.37; 0.49) |
| Patrono et al. 2021 [50] | US | All 45047 | GLP-1RAs 45047 | 71.5 | 6 | 0.98 (0.87; 1.10) | NA | 0.95 (0.81; 1.11) | 0.83 (0.64; 1.07) | 0.68 (0.59; 0.80) |
| Nakai et al. 2022 [47] | Japan | All 872 | DPP-4is 821 | \geq 75 | 12 | NA | NA | 0.68 (0.51; 0.90) | NA | 0.59 (0.47; 0.74) |
| Desai et al. 2022 [49] | US | Empagliflozin 11429 | Sitagliptin 11429 | 72 | 6 | NA | NA | 0.91 (0.67; 1.24) | NA | 0.67 (0.48; 0.92) |
| Desai et al. 2022 [49] | US | Empagliflozin 17502 | GLP-1RAs 17502 | 72 | 6 | NA | NA | 0.90 (0.71; 1.14) | NA | 0.85 (0.63; 1.13) |
| Htoo et al. 2022 [48] | US | Empagliflozin 22812 | Sitagliptin 22812 | 72 | 5 | 0.68 (0.60; 0.77) | NA | 0.64 (0.53; 0.78) | NA | 0.45 (0.36; 0.56) |
| Htoo et al. 2022 [48] | US | Empagliflozin 22894 | Liraglutide 22894 | 72 | 5 | 0.90 (0.79; 1.03) | NA | 0.97 (0.79; 1.17) | NA | 0.66 (0.52; 0.82) |

DPP-4is: dipeptidyl peptidase-4 inhibitors. GLP1RAs: glucagon-like peptide-1 receptor agonists. hHF: hospitalization for heart failure. MACE: major cardiovascular adverse events. NA: not available. SGLT2i: sodium-glucose cotransporter type 2 inhibitor.

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