Editorial Commentary

Does race/ethnicity influence the impact of new glucose-lowering agents on cardiovascular outcomes?—a comparison between Asian versus White patients

André J. Scheen[1,2]

[1]Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, CHU Liège, Liège, Belgium; [2]Division of Clinical Pharmacology, Center for Interdisciplinary Research on Medicines (CIRM), Liège University, Liège, Belgium

Correspondence to: André J. Scheen. Division of Diabetes, Nutrition and Metabolic Disorders, CHU Liège, B-4000 Liège, Belgium. Email: andre.scheen@chuliege.be.

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Introduction

Cardiovascular disease (CVD) represents a major burden in patients with type 2 diabetes (T2DM), with at least a twofold increase in myocardial infarction and ischemic stroke, and a major increase in heart failure (HF) as well, leading to reduced quality of life, recurrent hospitalisations and premature death. Asian patients with T2DM are also at increased risk of CVD (1). Two classes of glucose-lowering agents have proven their efficacy in reducing major cardiovascular adverse events [MACEs; nonfatal myocardial infarction, nonfatal stroke, cardiovascular (CV) mortality]: sodium-glucose cotransporter type 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) (2). Several reports compared the efficacy of the two pharmacological approaches and emphasized the existence of some crucial differences between these two drug families (3-6). Both classes now occupy a preferred place in the algorithm for the management of T2DM, especially in patients at high or very high CV risk (7). In those people with atherosclerotic CVD, international guidelines propose to use either an SGLT2i or a GLP-1RA whereas in patients with HF and/or chronic kidney disease the preference is given to SGLT2is owing to the overwhelming evidence issued from several placebo-controlled prospective cardiorenal outcome trials (7,8). Because many cardiovascular outcome trials (CVOTs) had a representation of South Asian cohorts, a similar consensus statement has been proposed by the South Asian Health Foundation (9) and also by a panel from the Asian Pacific Society of Cardiology (10).

In the last decade, emphasis has been put on a personalized approach for guiding pharmacotherapy in patients with T2DM. In absence of clear-cut evidence issued from genotyping studies so far (11), a phenotypic strategy is mostly recommended (12). Besides demographic characteristics (e.g., age, body mass index), biological parameters (e.g., glycated haemoglobin, glomerular filtration rate), drug safety profiles (e.g., risk of hypoglycaemia, gastrointestinal tolerance), the presence of comorbidities such as atherosclerotic CVD, HF or chronic kidney disease currently plays a major role in the selection of glucose-lowering agents in people with T2DM with the key objective to improve the overall prognosis of at risk patients (7,9,10).

The prevalence of T2DM in the Asian population is rapidly increasing and becomes a major burden in health care system (1). East Asian patients present specificities when analysing the characteristics of T2DM, for instance regarding the respective role of decreased insulin secretion and increased insulin resistance, which may influence the metabolic efficacy of the different glucose-lowering agents (13). Nevertheless, the race influence (Asian versus non-Asian) on the overall metabolic responses, especially the reduction in glycated haemoglobin, appeared rather limited for both SGLT2is (14,15) and GLP-1RAs (16). Asian

Table 1 Effects of SGLT2is on MACEs and CV death/hHF in Asian versus White patients

References	Trials	Patients	HR, Asians	HR, Whites	P for interaction
MACEs					
Singh *et al.* 2020 (19)	3 trials	4,987 Asians	0.88 (0.67–1.15)	NA	NA
Lee *et al.* 2021 (20)	4 trials (subgroup comparison)	3,298 Asians versus 20,258 Whites	0.81 (0.57–1.04)	0.90 (0.80–1.00)	0.46
CV death/hHF					
Singh *et al.* 2020 (19)	3 trials	4,987 Asians	0.86 (0.55–1.36)	NA	NA
Lee *et al.* 2021 (20)	2 trials (subgroup comparison)	1,788 Asians versus 5,962 Whites	0.60 (0.47–0.74)	0.82 (0.73–0.92)	0.01
Anker *et al.* 2021 (21)	1 trial (subgroup comparison)	824 Asians versus 4,542 Whites	0.65 (0.46–0.92)	0.81 (0.69–0.94)	0.33

Results are expressed as HR with 95% CI. SGLT2is, sodium-glucose cotransporter type 2 inhibitors; MACEs, major cardiovascular adverse events; CV, cardiovascular; hHF, hospitalisation for heart failure; HR, hazard ratio; NA, not available; CI, confidence interval.

patients with T2DM have also a different risk profile when considering the classical CV risk factors when compared to White people (17). Both SGLT2is and several GLP-1RAs were associated with reduced CV risk in Asian T2D patients (18). However, the impact of race/ethnicity on the efficacy of glucose-lowering agents such as SGLT2is and GLP-1RAs on CV complications has not been extensively studied so far. Some preliminary results of CVOTs suggested Asians may derive greater benefit than Whites from newer classes of antihyperglycaemic medications, especially GLP-1RAs (19).

In this invited editorial commentary, we will discuss a recent report of meta-analyses of CVOTs that compared CV effects of SGLT2is and GLP-1RAs in Asian versus White patients with and without T2DM (20). We will compare these results with what was already known regarding this topic. Ethnic heterogeneity of the Asian population with T2DM and the need for dedicated pharmacogenetic/pharmacogenomic studies will be emphasized. Such approaches together with careful race/ethnic interpretation of CVOT results may impact future therapeutic recommendations regarding the use of new glucose-lowering agents in the management of patients with T2DM at risk for CVD and HF.

Highlights of meta-analyses by Lee *et al.* (20)

A systematic review was performed of randomized placebo-controlled CVOTs of SGLT2is and GLP-1RAs that reported hazard ratio (HR) with 95% confidence interval (CI) for MACEs in patients with T2DM and for CV death/hospitalization for heart failure (hHF) in patients with reduced left ventricular ejection fraction (LVEF) (patients with or without T2DM) stratified by race (Asian versus White) (20). In four CVOTs comparing SGLT2is with placebo in patients with T2DM, the MACE outcome HR values were almost similar among Asians and Whites (P interaction =0.46) (*Table 1*). In contrast, in six CVOTs that compared GLP-1RAs with a placebo, the HR for MACE was lower in Asians (HR =0.68; 95% CI: 0.53–0.84) than in Whites (HR =0.87; 95% CI: 0.81–0.94) (P interaction =0.03) (*Table 2*). This means that GLP-1RAs are associated with a ≈2.5-fold larger relative risk reduction (32% versus 13%) for the MACE endpoint in Asians compared to Whites. In two SGLT2i trials in patients with HF and reduced LVEF, the CV death/hHF outcome HR was significantly lower in Asians (HR =0.60; 95% CI: 0.47–0.74) compared to Whites (HR =0.82; 95% CI: 0.73–0.92) (P interaction =0.01) (*Table 1*).

The conclusion was that compared with Whites, Asians may derive greater CV death/hHF benefit from SGLT2is in patients with HF and reduced LVEF. Regarding MACEs, Asian patients with T2DM may exhibit a greater benefit from GLP-1RAs in comparison to White patients, but no significant between-race difference could be detected for SGLT2is (20). The authors proposed different possible explanations for these race-based differences but all are speculative, in absence of more detailed information about baseline patient risk profile, adherence to therapy, use of co-medications, …

Table 2 Effects of GLP-1RAs on MACEs in Asian versus White patients

References	Trials	Patients	HR, Asians	HR, Whites	P for interaction
MACEs					
Singh *et al.* 2020 (19)	7 trials	4,298 Asians	0.71 (0.59–0.86)	NA	NA
Kang *et al.* 2019 (22)	3 trials (subgroup comparison)	2,625 Asians versus 21,149 Whites	0.35 (0.09–1.32)	0.92 (0.84–1.01)	<0.001
Lee *et al.* 2021 (20)	6 trials (subgroup comparison)	4,195 Asians versus 37,530 Whites	0.68 (0.53–0.84)	0.87 (0.81–0.94)	0.03

Results are expressed as HR with 95% CI. GLP-1RAs, glucagon-like peptide-1 receptor agonist; MACEs, major cardiovascular adverse events; HR, hazard ratio; NA, not available; CI, confidence interval.

The authors recognized some limitations of their analyses inherent to the available reported data and CVOT designs, lack of individual patient-level data, post-hoc subgroup analyses and relatively short duration of trial observation (20). Furthermore, the numbers of Asian patients were much lower compared to Whites in all CVOTs with SGLT2is or GLP-1RAs and only two CVOTs could be taken into account for patients with HF treated with SGLT2is. Finally, the interaction between Asian and White patients regarding the positive impact of GLP-1RAs on MACEs was only borderline significant. Thus, these results should be viewed as mainly exploratory rather than evidence-based.

CV risk in Asian patients with T2DM

CVD becomes a huge burden among Asian patients with T2DM. In a large observational study in a total of more than 1 million Asian individuals from different countries, patients with T2DM had a 1.89-fold risk of all-cause death compared with patients without diabetes (HR =1.89; 95% CI: 1.74–2.04), with a higher risk of coronary heart disease (HR =2.57; 95% CI: 2.19–3.02), and ischaemic stroke (HR =2.15; 95% CI: 1.85–2.51) (1). Comparisons with White patients led to contrasting results. South Asian people are two to four times more likely to develop T2DM than White individuals, but conversely do not experience more CV complications (23). Nevertheless, South Asian people, who represent a large, growing population in many European countries, have been shown to be at higher risk of developing not only T2DM, but also other risk factors such as atherogenic dyslipidaemia, leading to higher prevalence of coronary heart disease and stroke than in other ethnic groups living in Europe (17).

CV outcomes with new glucose-lowering agents

Evidence assessing therapeutic efficacy of new glucose lowering drugs in minority groups is limited and many CVOTs recruited rather few Asian patients or did not report specific ethnic data (20).

Preliminary data from meta-analyses of phase 2–3 RCTs

A meta-analysis of the events in the pooled analysis of phase 3 trials with SGLT2is (23,334 patients with T2DM) revealed that the reduction in the incidence of MACEs is statistically not significant (HR =0.83; 95% CI: 0.66–1.03; P=0.10), contrasting with a 64% statistically significant reduction in hHF (HR =0.36; 95% CI: 0.18–0.69; P<0.01) (24). This report did not separate Asian versus non-Asian patients. In a meta-analysis of a total of 17 trials with Asian patients and 39 trials with non-Asian patients, no disparity was found in the risk of all-cause mortality associated with SGLT2is treatment between Asian and non-Asian patients (25). No specific data were available regarding the incidence of MACEs or hHF in this report. Furthermore, these trials did not recruited patients at high CV risk and were generally of short duration (<1–2 years), so that the numbers of CV events were rather low and thereby these early studies were most probably underpowered to draw any definite conclusion. No similar comparative data were available for GLP-1RAs.

Data from meta-analyses of CVOTs

In contrast to phase 2–3 RCTs, CVOTs recruited a high number of patients at high CV risk and most of them were CV event-driven. According to a recent network meta-

analysis of placebo-controlled CVOTs, GLP-1RAs (and not SGLT2is) are the only drug class that reduces the risk of ischaemic stroke, a key component of 3-points MACEs (5). The meta-analyses of six CVOTs with GLP-1RAs reported by Lee *et al.* (20) suggested that Asian patients with T2DM may exhibit a greater reduction in MACEs with GLP-1RAs compared to White patients. No detailed data were presented regarding the individual components of 3-points MACEs. These findings confirm previous results. In a first meta-analysis of three CVOTs with GLP-1RAs (LEADER, SUSTAIN-6 and EXSCEL), overall, statistically significant risk reductions in MACEs and CV death were observed compared to the placebo groups. Of note, a significant racial difference with respect to CV benefit was noticed in a post-hoc subgroup analysis (P for interaction <0.001): indeed, more pronounced risk reductions were observed in Asians (RR =0.35; 95% CI: 0.09–1.32), with a significantly greater CV benefit from GLP-1 RA therapy, compared with White subjects (P<0.0001) (*Table 2*) (22). In another meta-analysis, a significant reduction in MACEs was noticed with GLP-1RAs but not with SGLT-2Is in Asians (19). This meta-analysis that focused on Asians only did not compare the results with those observed in White patients (*Table 2*).

The effects of SGLT2is on MACEs remain controverted, essentially due to the absence of positive effect on stroke, in contrast to what has been reported with GLP-1RAs (5). Of note, their positive effect on hHF appears impressive and has been consistently demonstrated in patients with and without T2DM (24). In a previous meta-analysis of three CVOTs, no significant reduction in MACEs but also in hHF or CV death could be demonstrated with SGLT2is in Asian patients with T2DM (19). As pointed out by the authors, it remains to show whether these results are related to an inadequate statistical power, explained by an underrepresentation of Asians, or a true ethnic difference. The results reported in the more recent meta-analysis by Lee *et al.* (20) confirmed only a numerical reduction in MACEs with SGLT2is compared to placebo (–19% in Asians versus –10% in Whites), with no significant interaction (*Table 1*). In contrast, a highly statistically significant reduction in hHF/CV mortality was observed in patients with HF and reduced LVEF, in both racial groups, with a greater reduction observed in Asians than in Whites (–40% versus –18%, P interaction <0.01) (*Table 1*) (20).

In the analysis by Lee *et al.* (20), only two CVOTs were available for the analysis of the race impact of SGLT2is in patients with HF and reduced LVEF (DAPA-HF and EMPEROR-Reduced). These results appeared to be confirmed in patients with HF and preserved LVEF as recently reported in EMPEROR-Preserved (21). The CV death/hHF primary outcome HR in 824 Asians versus 4,542 Whites was 0.65 (95% CI: 0.46–0.92) versus 0.81 (95% CI: 0.69–0.94), respectively.

Unanswered questions related to race/ethnic differences

Ethnic heterogeneity of Asian population

Asian people are recognized belonging to a heterogeneous population divided in several regions: East Asians, West Asians, South Asians, Central Asians, Southeast Asians. Such subgroups may have different genetic background and be exposed to various environmental conditions, which could impact the clinical characteristics of T2DM. Thereby, patients may respond differently to antidiabetic pharmacotherapies. As pointed out by Lee *et al.* (20), the reported meta-analyses are lacking of granular categorization of race within broadly defined Asian subgroups (South Asians and East/Southeast Asians were collectively categorized as Asians because of the way most CVOTs categorized race). Furthermore, definitions of race or ethnicity varied across CVOTs included in the meta-analyses (20). Available data suggested at least comparable and potentially greater outcome benefits in Asians in the vast majority of CVOTs with GLP-1RAs and SGLT2is. However, it was impossible to conclude whether the effects were similar across all Asian subgroups. Both trialists and clinical investigators should be encouraged to record ethnicity with better precision to allow data recorded in different ethnic subgroups to be better analysed (26). Among the Asian population, ethnicity may modify the association between T2DM and ischemic heart disease as shown when comparing Chinese, Malays and Asian Indians living in Singapore (27). Asian Indians are more susceptible to develop T2DM than Chinese and Malays and when diabetes mellitus occurs, the risk of ischaemic heart disease is higher than for their Chinese and Malays counterparts (28). Of note, a study reported that ≤15% of a nationally representative population of patients with T2DM in China would have been eligible for enrolment in three CVOTs with GLP-1RAs considered in a previous meta-analysis (22), thus questioning about the generalizability of CVOTs results to Chinese patients with T2DM (29).

Thus, more stringent assessment of the effects of either SGLT2is or GLP-1RAs on CV outcomes according to

different ethnicities among the Asian population might be helpful in order to refine guidelines for the management of T2DM in Asian individuals (30).

Need for pharmacogenetic/pharmacogenomic studies

Recent (epi)genome-wide association studies and metabolomic investigations among patients with atherosclerotic CVD and HF have identified genes, metabolites and pathways associated with CVD traits. However, these results were mostly driven by samples of European ancestry, a population that may not accurately represent the CVD risk at the molecular level and the specific clinical and biologic risk profile of CVD in South Asian people, especially those individuals with T2DM (31).

Pharmacogenomics has already demonstrated its potential for individualized drug therapy based on genetic and genomic information of patients. Thereby, it has made some progress in precision medicine and personalized drug therapy possible (32,33). However, most studies were devoted to the risk of drug adverse events rather than to potential CV protection (34). Furthermore, available information about new glucose-lowering agents GLP-1RAs and SGLT2is are still scarce and not related to CV outcomes (33). More comprehensive pharmacogenetic/pharmacogenomic research in various clinical settings, including in different ethnic groups among the Asian population, may clarify the potential gene-drug interactions and thereby refine therapeutic recommendations, a key step for optimisation of precision medicine (35).

Conclusions

In patients with T2DM, SGLT2is and GLP-1RAs reduced CV outcomes, yet with notable differences in benefits and harms. Meta-analyses of CVOTs suggest that Asian patients may profit to a greater extent from GLP-1RAs to reduce MACEs and from SGLT2is to reduce hHF-CV mortality composite outcome when compared to White patients. However, these conclusions should be taken with caution because they were derived from post-hoc analyses of placebo-controlled interventional studies that recruited a rather limited number of Asian patients from different ethnic origins. Overall, these findings are hypothesis generating. Further dedicated studies, including large observational studies well designed to compare CV outcomes in Asian (if possible, separated by ethnic subgroups) versus White patients treated with either a GLP-1RA or an SGLT2i would be of major interest to confirm these exploratory findings. Finally, pharmacogenetic/pharmacogenomic studies devoted to these new glucose-lowering agents and their effects on CV outcomes in Asian versus White patients with T2DM would be useful to make significant progress in precision medicine.

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Footnote

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