Meta-analyses of Results From Randomized Outcome Trials Comparing Cardiovascular Effects of SGLT2is and GLP-1RAs in Asian Versus White Patients With and Without Type 2 Diabetes

Matthew M.Y. Lee,[1] Nazim Ghouri,[1,2] Darren K. McGuire,[3] Martin K. Rutter,[4,5] and Naveed Sattar[1]

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META-ANALYSIS

BACKGROUND

Results of cardiovascular outcome trials (CVOTs) suggest Asians may derive greater benefit than Whites from newer classes of antihyperglycemic medications.

PURPOSE

To provide summary hazard ratio (HR) estimates for cardiovascular efficacy of sodium–glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide 1 receptor agonists (GLP-1RAs) stratified by race (Asian vs. White).

DATA SOURCES

A systematic review performed in PubMed from 1 January 2015 to 8 December 2020.

STUDY SELECTION

Randomized placebo-controlled CVOTs of SGLT2is and GLP-1RAs that reported HRs (95% CIs) for *1*) major adverse cardiovascular event (MACE) in patients with diabetes and *2*) cardiovascular (CV) death/hospitalization for heart failure (HHF) in patients with HF and reduced ejection fraction (HFrEF).

DATA EXTRACTION AND SYNTHESIS

HRs (95% CIs) for selected outcomes in Asians and Whites were extracted from each trial, adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Random-effects meta-analyses were performed to examine differences between the selected outcomes in Asians versus Whites.

RESULTS

In four SGLT2i trials in type 2 diabetes, the MACE outcome HR (95% CI) in 3,298 Asians versus 20,258 Whites was 0.81 (0.57, 1.04) vs. 0.90 (0.80, 1.00), respectively ($P_{interaction}$ = 0.46). In two SGLT2i trials in patients with HFrEF, the CV death/HHF outcome HR in 1,788 Asians versus 5,962 Whites was 0.60 (0.47, 0.74) vs. 0.82 (0.73, 0.92), respectively ($P_{interaction}$ = 0.01). In six GLP-1RA trials, the MACE outcome HR in 4,195 Asians versus 37,530 Whites was 0.68 (0.53, 0.84) vs. 0.87 (0.81, 0.94), respectively ($P_{interaction}$ = 0.03).

LIMITATIONS

Lack of individual patient–level data, relatively short duration of trial observation, and lack of granular categorization of race within broadly defined Asian subgroups.

CONCLUSIONS

Compared with Whites, Asians may derive greater CV death/HHF benefit from SGLT2is in patients with HFrEF, and MACE benefit from GLP-1RAs in patients with type 2 diabetes.

[1]*Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, U.K.*
[2]*Department of Diabetes and Endocrinology, Queen Elizabeth University Hospital, Glasgow, U.K.*
[3]*University of Texas Southwestern Medical Center, Parkland Health and Hospital System, Dallas, TX*
[4]*Division of Diabetes, Endocrinology and Gastroenterology, School of Medical Sciences, University of Manchester, Manchester, U.K.*
[5]*Diabetes, Endocrinology and Metabolism Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, U.K.*

Corresponding author: Naveed Sattar, naveed.sattar@glasgow.ac.uk

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Randomized trial results and their meta-analyses have demonstrated the cardiovascular (CV) benefits of novel antihyperglycemic medications for type 2 diabetes such as sodium-glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide 1 receptor agonists (GLP-1RAs) (1,2). Furthermore, certain populations such as Asians, which form nearly 60% of the world's population, including South Asians and East/Southeast Asians (here collectively categorized as Asian because of the way most trials categorize race), experience a greater burden of type 2 diabetes compared with Whites, although they vary markedly in their risk of atherosclerotic CV disease (3,4). Results from a recent meta-analysis pooling data for Asians with type 2 diabetes also indicated a significant reduction in major adverse CV events (MACE) with GLP-1RAs but not with SGLT2is, compared with placebo. However, this study did not directly compare Asians versus Whites and did not consider all relevant SGLT2i trials (5).

In the present report, we meta-analyzed summary hazard ratio (HR) estimates from CV outcome trials (CVOTs) of SGLT2is and GLP-1RAs for effect modification of the efficacy of study drugs by race (Asian vs. White) with regard to selected CV outcomes. Of the antihyperglycemic drug classes, SGLT2is and GLP-1RAs are the only ones to show consistent benefits in CV outcomes, and therefore, we set out to examine these two drug classes only.

RESEARCH DESIGN AND METHODS

Data Sources and Searches

A systematic review was performed in PubMed from 1 January 2015 to 8 December 2020 to identify published large randomized placebo-controlled trials of SGLT2is and GLP-1RAs (6). Our search strategy is detailed in our Supplementary Fig. 1, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

Study Selection

Inclusion criteria included CVOTs of SGLT2is and GLP-1RAs providing effect size estimates (HRs [95% CIs]) in the subgroups of interest (i.e., Asians and Whites) for the outcomes of *1*) MACE in patients with type 2 diabetes, and *2*) CV death/hospitalization for heart failure (HHF) in patients with HF and reduced ejection fraction (HFrEF).

Data Extraction and Quality Assessment

HRs (95% CIs) for the outcomes of interest in Asians and Whites were extracted from each study by at least two researchers independently, adhering to PRISMA guidelines (7). Risk of bias was assessed using version 2 of the Cochrane risk-of-bias tool for randomized trials (8) (Supplementary Fig. 2).

Data Synthesis and Analysis

We used the statistical software Stata/SE 16.0, using the Stata command "meta" to perform a random-effects model (DerSimonian and Laird method) meta-analysis (9). Our primary analyses compared CV outcomes reported by race of Asian and White, in addition to tests for group differences ($P_{interaction}$).

RESULTS

We identified 11 SGLT2i trials and 7 GLP-1RA trials (10–26) (Supplementary Fig. 1 PRISMA diagram).

Two SGLT2i trials (DECLARE-TIMI 58 and SOLOIST-WHF) were excluded because the HR (95% CI) was not available for the subgroups of Asian and White patients (18,19). In SOLOIST-WHF, in the Asian subgroup, the HR could not be estimated because of 0 events in one of the treatment groups (19). Two other SGLT2i trials in patients with chronic kidney disease (CREDENCE and DAPA-CKD) were excluded because the reported outcomes available for Asian versus White patients were not MACE or CV death/HHF (13,14). One SGLT2i trial (SCORED) was excluded because it had a different population (i.e., not HF) from the other two trials that reported the CV death/HHF outcome (15).

Six trials of SGLT2is were analyzed (Table 1); four diabetes trials (EMPA-REG OUTCOME, CANVAS Program [CANVAS and CANVAS-R], and VERTIS CV) reported MACE, and two HF trials (Dapa-HF and EMPEROR-Reduced) reported CV death/HHF (10–12,16–17).

In four SGLT2i outcome trials including 3,298 Asian and 20,258 White patients with type 2 diabetes, the HR (95% CI) for the MACE outcome in Asian versus White patients was 0.81 (0.57, 1.04) vs. 0.90 (0.80, 1.00), respectively ($P_{interaction}$ = 0.46) (Fig. 1).

In two SGLT2i outcome trials including 1,788 Asian and 5,962 White patients with HF and reduced ejection fraction (HFrEF), the HR (95% CI) for CV death/HHF in Asian versus White patients was 0.60 (0.47, 0.74) vs. 0.82 (0.73, 0.92), respectively ($P_{interaction}$ = 0.01) (Fig. 2).

One GLP-1RA trial (ELIXA) was excluded because the HR (95% CI) was not extractable for the subgroups of Asian and White patients (20).

Six trials of GLP-1RAs were analyzed (Table 1); LEADER, SUSTAIN-6, EXSCEL, HARMONY OUTCOMES, REWIND, and PIONEER 6 (21–26) reported MACE.

In six GLP-1RA trials with 4,195 Asian and 37,530 White patients, the HR (95% CI) for the MACE outcome in Asian versus White patients was 0.68 (0.53, 0.84) vs. 0.87 (0.81, 0.94), respectively ($P_{interaction}$ = 0.03) (Fig. 3).

CONCLUSIONS

Results of clinical outcome trials of SGLT2is and GLP-1RAs comparing CV outcomes in Asians versus Whites suggest differential treatment effects of SGLT2is (in those with HFrEF) and GLP-1RAs by race, with greater benefits of both classes in Asians. Because the interaction between Asian race and outcome seems consistent across different groups of studies, particular for the GLP-1RA class, it seems unlikely that random variation in baseline characteristics between trial arms explains the results.

The recent meta-analysis by Singh and Singh (5) of three SGLT2i trials found no significant reduction in MACE, HHF, or CV death in Asians and postulated whether these results were due to low statistical power, underrepresentation of Asians, or true ethnic difference. However, there seems to be benefit in terms of reduction in risk of CV death/HHF when the two HFrEF trials are meta-analyzed. This suggests that SGLT2is lessen risk in Asians at least as well as in Whites and potentially better in patients with HFrEF. Perhaps more significantly, we show GLP-1RA–derived MACE benefits are significantly ($P_{interaction}$ = 0.03) better in Asians (mean [95% CI] risk reduction 32% [16–47%]) than in Whites (13% [6–19%]), with remarkably lower HRs in Asians versus Whites in all six trials. That is, GLP-1RAs have an ~2.5-fold larger relative risk reduction for the MACE end point in Asians compared with Whites.

These findings are all hypothesis generating, and several limitations should be considered before concluding that such therapies, particularly GLP-1RAs, lessen MACE risks more in Asians. Firstly, the Asian subpopulation is often derived

Table 1—SGLT2i and GLP-1RA trials

Trial	Year	Population	Primary outcome	Events/patients, *n*/*N* Asian Treatment	Events/patients, *n*/*N* Asian Placebo	Events/patients, *n*/*N* White Treatment	Events/patients, *n*/*N* White Placebo	Total Patients, *N* Asian	Total Patients, *N* White
SGLT2i primary MACE outcome trials (3,298 Asian + 20,258 White)									
EMPA-REG OUTCOME (10)	2015	Type 2 diabetes and high CV risk	Composite of CV death/nonfatal MI/nonfatal stroke	79/1,006	58/511	366/3,403	205/1,678	1,517	5,081
CANVAS Program* (11)	2017	Type 2 diabetes and high CV risk	Composite of CV death/nonfatal MI/nonfatal stroke	NR	NR	NR	NR	1,284	7,944
VERTIS CV (12)	2020	Type 2 diabetes and ASCVD	MACE (composite of CV death/nonfatal MI/nonfatal stroke)	36/336	19/161	573/4,820	278/2,413	497	7,233
SGLT2i primary CV death/HFH outcome trials (1,788 Asian + 5,962 White)									
Dapa-HF (16)	2019	HFrEF, with and without type 2 diabetes	Composite of worsening HF (hospitalization or urgent visit resulting in IV therapy for HF)/CV death	78/552	118/564	275/1,662	348/1,671	1,116	3,333
EMPEROR-Reduced (17)	2020	HFrEF, with and without type 2 diabetes	Composite of CV death/hospitalization for worsening HF	62/337	99/335	264/1,325	289/1,304	672	2,629
GLP-1RA primary MACE outcome trials (4,195 Asian + 37,530 White)									
LEADER (21)	2016	Type 2 diabetes and high CV risk	First occurrence of CV death/nonfatal MI/nonfatal stroke	40/471	56/465	494/3,616	543/3,622	936	7,238
SUSTAIN-6 (22)	2016	Type 2 diabetes and high CV risk	First occurrence of CV death/nonfatal MI/nonfatal stroke	8/121	17/152	93/1,384	118/1,352	273	2,736
EXSCEL (23)	2017	Type 2 diabetes with or without previous CV disease	First occurrence of CV death/nonfatal MI/nonfatal stroke	60/725	74/727	683/5,554	712/5,621	1,452	11,175
HARMONY OUTCOMES (24)	2018	Type 2 diabetes and CV disease	First occurrence of CV death/MI/stroke	13/228	19/242	248/3,295	323/3,288	470	6,583
REWIND (25)	2019	Type 2 diabetes with previous CV disease or CV risk factors	First occurrence of nonfatal MI/nonfatal stroke/death from CV causes or unknown causes	21/216	30/218	462/3,754	505/3,744	434	7,498
PIONEER 6 (26)	2019	Type 2 diabetes and high CV risk	First occurrence of MACE (CV death/nonfatal MI/nonfatal stroke)	9/324	19/306	46/1,148	55/1,152	630	2,300

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; IV, intravenous; MI, myocardial infarction; NR, not reported. *CANVAS Program comprises two trials, CANVAS and CANVAS-R.

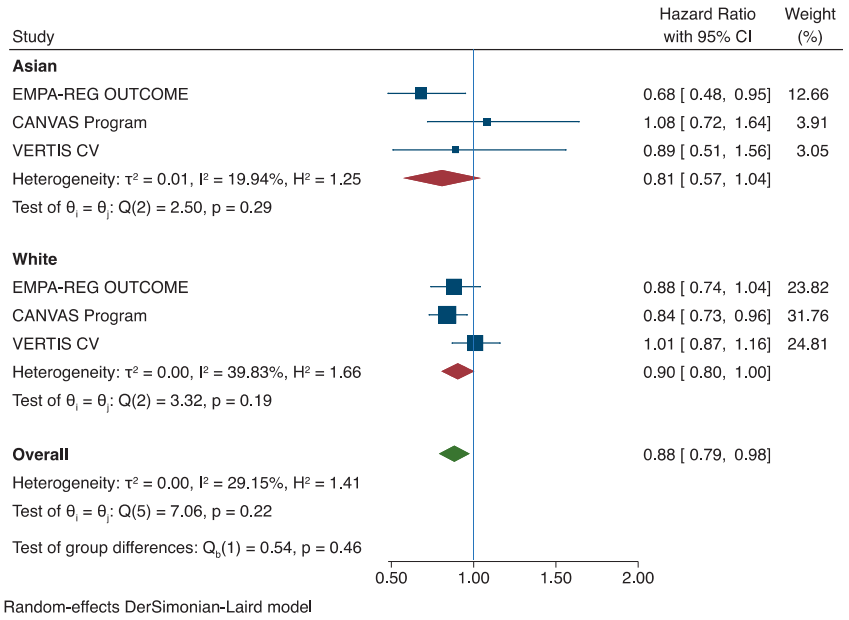

Figure 1—SGLT2i CVOTs reporting risk for MACE outcome by race.

from several countries that collectively have a heterogeneous racial makeup, including East, South East, and South Asian subgroups. Although all Asian subgroups are at elevated type 2 diabetes risk compared with Whites, their atherosclerotic CV disease risk can vary markedly, being higher in South Asians versus Whites but lower in other Asian subgroups (4). However, the findings are complex; we noted lower CV mortality in South Asians compared with Whites in a recent observational study of people with type 2 diabetes (27). Furthermore, because of a lack of breakdown of baseline characteristics by race in trials, it is not known to what extent Asian populations were treated or pretreated with standard preventative therapies in each of the trials examined. It is possible that some Asian subgroups were less likely to receive comparative preventive therapy compared with Whites, leading to an apparent accentuated benefit seen with SGLT2i and/or GLP-1RA therapy in this group, although even if this were true, such an observation would be clinically important.

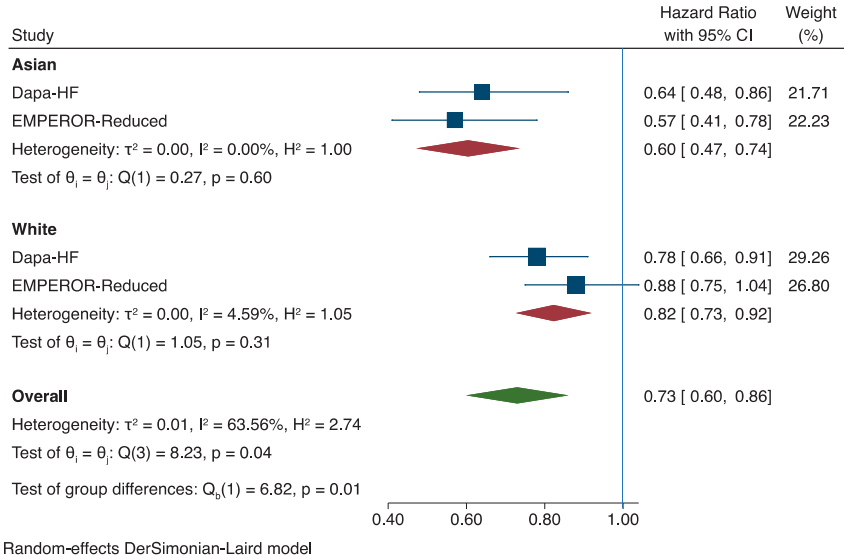

Figure 2—SGLT2i CVOTs reporting risk for CV death/HHF outcome by race.

Alternatively, there may be other genuine biological explanations for these differences that merit future investigation. For example, because diabetes onset is far earlier in Asian subgroups and occurs at lower BMI (28,29), it may be that MACE or other cardiac risks driven by glycemia-affected pathways are more pronounced in Asian groups and that such pathways are better targeted by novel diabetes therapies. This is speculative, however, and more work is needed to determine if differences are genuine and, if so, identify potential mechanisms, including effects on multiple risk pathways.

There may have been differences in the proportion of Asian versus White patients with type 2 diabetes and chronic kidney disease within the HF trials, although this information was not routinely available. A recent meta-analysis by Zannad et al. (30) of the two SGLT2i trials in patients with HFrEF showed no clear difference in outcome by either diabetes status or eGFR levels $\geq$ or $<$60 mL/min/1.73 m^2. Therefore, it seems unlikely that these characteristics explain any potential differences in CV death/HHF outcomes by ethnicity.

Our meta-analysis has several limitations. Detailed analyses of specific subpopulations of Asians are not possible from these trials because of limitations of relevant data collection. There was heterogeneity between the studies, particularly in the SGLT2i outcome trials, with I^2 ranging from 0% to $>$60%. That noted, there was far less heterogeneity within Asian and White groups in the analyses for which we report differences, namely for SGLT2is and HF and in the GLP-1RA analysis (I^2 up to maximum of 28.6%). Although not definitive, these findings lend some confidence to the findings we report. The primary outcomes varied among the five diabetes CVOTs versus two HF trials. Although trials reported data on Asians, as mentioned, data were lacking on more specific subgroups (e.g., South, East, and Southeast Asians). Definitions of race or ethnicity varied (reported by patients in VERTIS CV, EMPEROR-Reduced, LEADER, EXSCEL, HARMONY OUTCOMES, and REWIND; reported by investigators in Dapa-HF; reported by investigator inquiry of participants in CANVAS Program; and not clearly specified in EMPA-REG OUTCOME, SUSTAIN-6, or PIONEER 6). Our main goal, as predefined

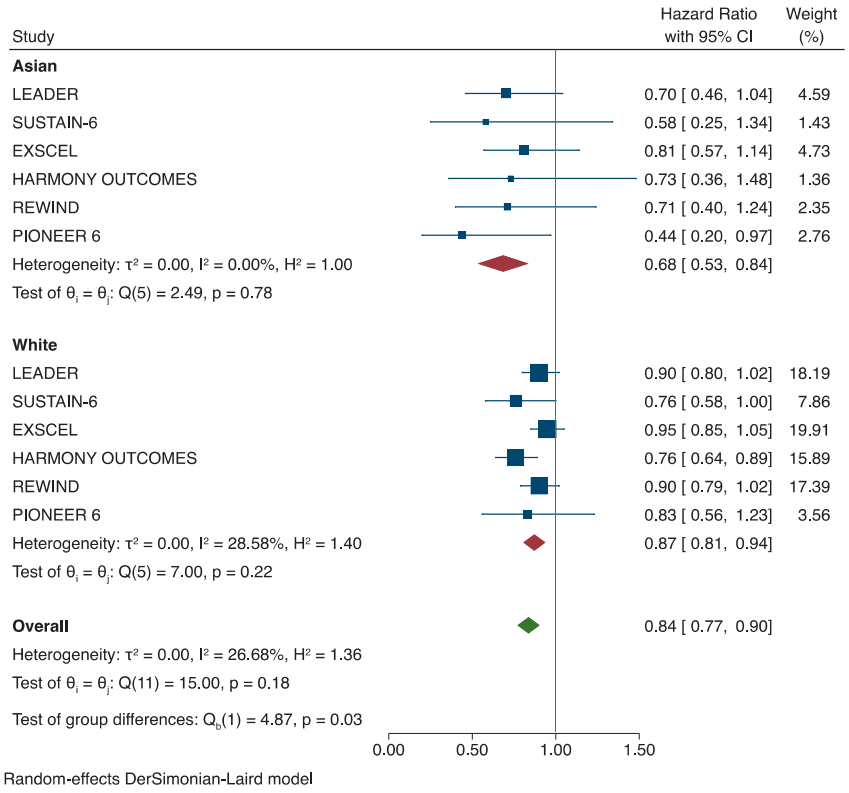

Figure 3—GLP-1RA CVOTs reporting risk for MACE outcome by race.

in PROSPERO, was to examine Asians versus Whites, and therefore, other races and ethnic groups were not analyzed. However, we feel that examining differences in other races and ethnic groups should form the basis of a separate report. Finally, individual patient–level data were not used for analyses, and therefore, we could not adjust for potential important differences such as duration of diabetes, baseline treatment, or baseline characteristics such as BMI or smoking history, which vary between groups and could have affected MACE and CV death/HHF outcomes.

Going forward, we suggest an individual participant meta-analysis would be informative when all trial data are made available, including looking at the risk of adverse effects by ethnic group. It might also be of interest to examine adherence to therapy and the proportion of people who complete a trial or drop out by ethnic group. For example, it might be that Asians recruited to CVOTs are more compliant with therapy than Whites. Such possibilities could also be assessed through secondary analyses.

In conclusion, there is an apparent greater benefit of GLP-1RA therapy in Asians compared with Whites across all types of GLP-1RAs so far tested. In addition, in Asians, SGLT2is have at least as good an effect on MACE and potentially better effect on CV death/HHF outcomes compared with Whites. For future trials to be more informative, Asian race needs to be recorded with greater granularity, rather than grouping by geographical region. In particular, Asian race (a grouping that now covers nearly 60% the world's population) should be broken down into more specific groups. We also suggest a need for more outcome-specific trials in Asian countries to further explore and validate the findings for GLP-1RAs. The findings of these analyses are relevant to the design, data capture, and reporting of future CVOTs.

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