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RESEARCH LETTER

Are novel glucose-lowering agents' cardiorenal benefits generalizable to individuals of Black race? A meta-trial sequential analysis to address disparities in cardiovascular and renal outcome trials enrolment

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1 | BACKGROUND

Racial and ethnic diversity in clinical trials serves as a metric of societal equality and access to healthcare. Unfortunately, as in most large-scale studies of cardiovascular (CV) benefits/risks, the Black populations have been vastly under-represented, creating challenges in interpreting underpowered subgroup analyses from individual trials.[1] Limited generalizability of the trial findings may perpetuate disparities in clinical outcomes by precluding precision health approaches.

To date, evidence from CV and renal outcome trials and their meta-analyses have shown that treatment with sodium-glucose co-transporter-2 (SGLT2) inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1RAs) provides cardiorenal benefits among individuals with or without type 2 diabetes (T2D).[2] However, it remains unclear whether the cardiorenal benefits of the newer agents are generalizable to racial and ethnic minority groups. Thus, in this study, we conducted a meta-analysis of CV and renal outcome trials to determine the effects of dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1RAs, and SGLT2 inhibitors on cardiorenal outcomes in Black and White participants with or without T2D. We further applied trial sequential analysis to determine whether the sample size available for Black participants was deemed of sufficient power to reach a reliable conclusion.

Racial/ethnic diversity in research, especially in clinical trials that establish standards of care, is necessary to minimize disparities in outcomes and to uphold societal equity in healthcare.[1] This study intended to address an omnipresent failure in the chain of health equity: under-enrolment of socially disadvantaged populations in key clinical trials of potentially life-saving treatments and its negative consequences on the external validity, equality, and scientific rigour of research.

2 | METHODS

PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched from inception up to 28 March 2021 according to a predesigned search strategy (Table S1). Two reviewers (HT and WS) independently selected potential trials

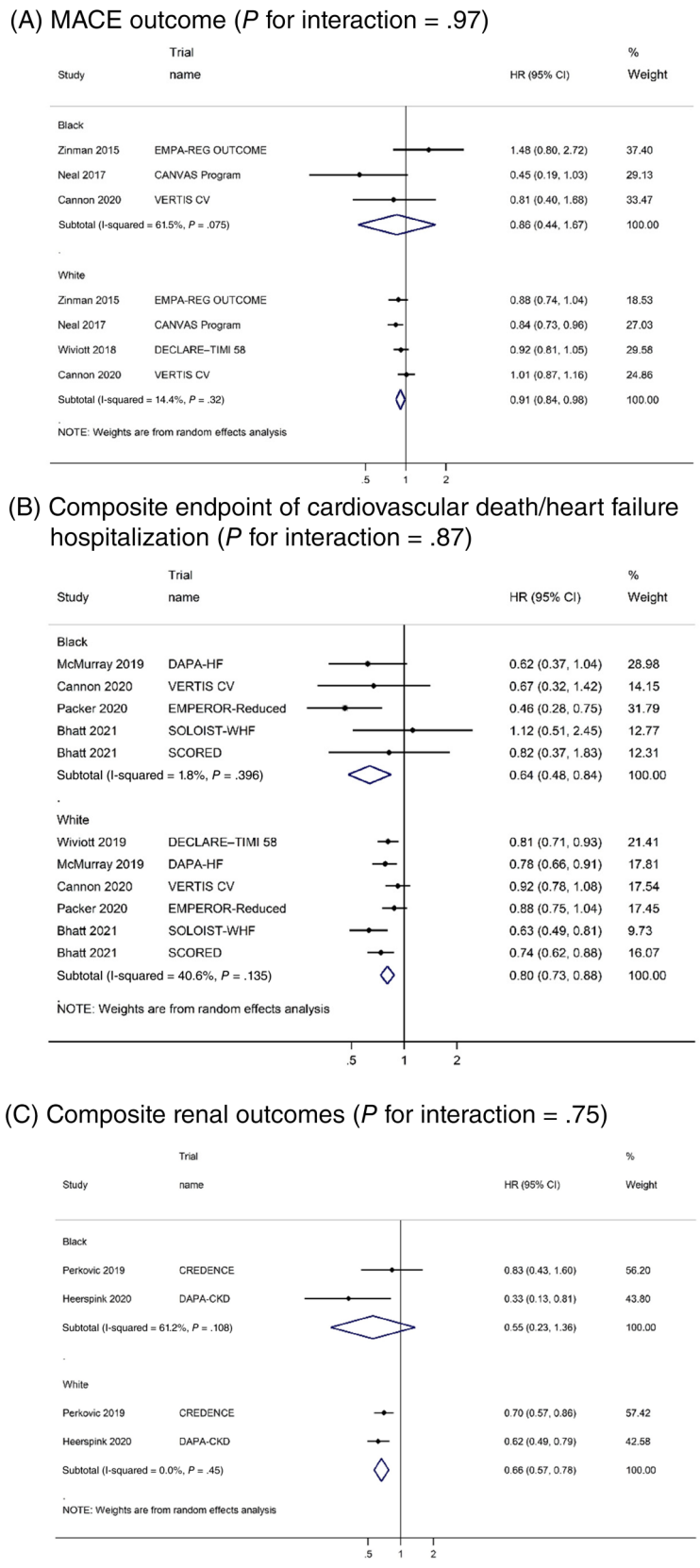

FIGURE 1 Meta-analysis of the effects of sodium-glucose co-transporter-2 inhibitors on A, major adverse cardiovascular events (MACE), B, Composite endpoint of heart failure hospitalization or cardiovascular death, and C, composite renal outcomes, by race. HR, hazard ratio. Wiviott 2018 (DECLARE-TIMI 58) reported the outcomes among the White subgroup only

based on the following inclusion criteria: (a) CV and renal outcome trials designed to evaluate the effects of novel glucose-lowering agents on CV or renal outcomes; (b) trials investigating DPP-4 inhibitors, GLP-1RAs, and SGLT2 inhibitors; and (c) trials reporting MACE, composite endpoint of CV death/heart failure hospitalization (HHF), or composite renal outcomes (including end-stage kidney disease, a

sustained decline in the estimated glomerular filtration rate, death from renal or CV causes, or a doubling of the serum creatinine level) in explicit strata of Black or White adults (aged ≥18 years) with or without T2D. The detailed definitions of these outcomes by each trial are presented in Table S2.

Two authors (HT and WS) independently extracted data on study design, patients' characteristics, type of intervention, and outcomes. If outcome data were unavailable in original trial publications, we extracted these data from one previous meta-analysis.[3] We also assessed the risk of bias of included trials according to the Cochrane risk of bias tool. Disagreement was resolved through consensus.

Within each of the two racial groups (White and Black), we individually assessed the effects of each class of glucose-lowering agents (DPP-4 inhibitors, GLP-1RAs, or SGLT2 inhibitors) compared with the control group (placebo or glimepiride) on the risk of the following three outcomes: MACE, composite endpoint of CV death/HHF, and composite renal outcomes. We calculated a pooled HR and 95% CI using a random-effects model. Statistical heterogeneity between studies was estimated using I^2 statistic with upper limits of 25%, 50%, and 75% indicating low, moderate, and high, respectively. For each drug class, we performed a meta-regression including an interaction term between race and treatment to assess the differences in the treatment effect by race (Black vs. White) and carried out a sensitivity analysis limited to trials reporting outcomes for both Black and White participants to test the robustness of the evidence. We applied the GRADE approach to assess the overall quality of the evidence[4] and employed the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) to access the quality of subgroup effects.[5] Finally, we applied a trial sequential analysis to calculate the required information size that would confer a statistical power of 80% to detect a 15% relative risk reduction in the risk of cardiorenal outcomes, with an alpha-error level of .05. Statistical analyses were performed using STATA (version 14; Stata Corp., College Station, TX) and TSA 0.9.5.10 beta (https://ctu.dk/tsa/downloads/).

3 | RESULTS

The structured literature search retrieved 9648 citations from electronic databases and identified 22 CV and renal outcome trials that reported the CV or renal outcomes in Black and/or White participants (five for DPP-4 inhibitors, seven for GLP-1RAs, and 10 for SGLT2 inhibitors) (see references in Table S3). The 22 trials included a total of 175 893 participants, among whom 7944 (4.5% of total trial participants) were identified as Black race. One trial reported the outcomes in White but not in Black participants,[6] while one trial in Black but not

TABLE 1 GRADE summary of findings and certainty of the evidence

Outcomes	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
SGLT2 inhibitors			
MACE-Black	HR 0.86 (0.44-1.67)	928 (3 trials)	⊕⊕⊕⊖ **Moderate**[a]
MACE-White	HR 0.91 (0.84-0.98)	33 718 (4 trials)	⊕⊕⊕⊕ **High**
CV death/HHF-Black	HR 0.64 (0.48-0.84)	1132 (5 trials)	⊕⊕⊕⊕ **High**
CV death/HHF-White	HR 0.80 (0.73-0.88)	36 543 (6 trials)	⊕⊕⊕⊕ **High**
Composite renal outcomes-Black	HR 0.55 (0.23-1.36)	415 (2 trials)	⊕⊕⊕⊖ **Moderate**[a]
Composite renal outcomes-White	HR 0.66 (0.57-0.78)	5221 (2 trials)	⊕⊕⊕⊕ **High**
GLP-1RAs			
MACE-Black	HR 0.92 (0.67-1.26)	3191 (7 trials)	⊕⊕⊕⊕ **High**
MACE-White	HR 0.90 (0.83-0.98)	42 106 (7 trials)	⊕⊕⊕⊕ **High**
DPP-4 inhibitors			
MACE-Black	HR 0.91 (0.68-1.04)	1910 (5 trials)	⊕⊕⊕⊕ **High**
MACE-White	HR 0.97 (0.91-1.04)	32 367 (4 trials)	⊕⊕⊕⊕ **High**
Composite renal outcomes-Black	HR 1.31 (0.80-2.14)	411 (1 trial)	⊕⊕⊕⊖ **Moderate**[b]
Composite renal outcomes-White	HR 1.03 (0.86-1.24)	5596 (1 trial)	⊕⊕⊕⊖ **Moderate**[b]

Note: GRADE Working Group grades of evidence: **High quality:** further research is highly unlikely to change our confidence in the estimate of effect. **Moderate quality:** further research is probable to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** further research is highly probable to have an important impact on our confidence in the estimate of effect and is probable to change the estimate. **Very low quality:** we are very uncertain about the estimate.

Abbreviations: CI, confidence interval; CV death/HHF, cardiovascular death or heart failure hospitalization; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; HR, hazard ratio; GLP-1RAs, glucagon-like peptide-1 receptor agonists; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; MACE, major adverse cardiovascular events; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors.

[a]Downgraded one level because of inconsistency (e.g. statistical hetereogenity between trials).

[b]Downgraded one level because of imprecision (e.g. only one trial included).

in White populations.[7] The basic characteristics and definitions in CV and renal outcomes for each trial are presented in Tables S3 and S2, respectively.

Four SGLT2 inhibitor outcome trials reported the outcome of MACE (three for Black participants and four for White participants) (Figure 1). The HR for Black participants and White participants was 0.86 (0.44, 1.67) and 0.91 (0.84, 0.98), respectively, with a *P* for interaction of .97. The composite endpoint of CV death/HHF was available in six trials (five trials for Black participants and six trials for White participants) (Figure 1). SGLT2 inhibitors were associated with a decreased risk by 36% in Black participants (HR, 0.64; 95% CI, 0.48-0.84) and by 20% in White participants (HR, 0.80; 95% CI, 0.73-0.88). There was no significant difference in treatment effect between Black participants and White participants (*P* for interaction = .87). Similar results for MACE outcome and composite endpoint of CV death/HHF were found in the sensitivity analysis limited to trials reporting outcomes for both Black and White participants (Figure S2). Of two trials reporting composite renal outcomes, SGLT2 inhibitors reduced the risk by 45% in Black participants (HR, 0.55; 95% CI, 0.23-1.36) and by 34% in White participants (HR, 0.66; 95% CI, 0.57-0.78) (*P* for interaction = .75) (Figure 1).

Seven trials reported MACE outcome for GLP-1RAs. GLP-1 RAs were not significantly associated with a decreased risk in Black participants (HR, 0.92; 95% CI, 0.67-1.26), while GLP-1RAs significantly reduced this risk in White participants (HR, 0.90; 95% CI, 0.83-0.98), with a *P* for the interaction of .77 (Figure S3).

MACE outcome was assessed in five DPP-4 inhibitor trials (five trials for Black participants and four for White participants). DPP-4 inhibitors were not significantly associated with a decreased risk of MACE in both Black participants (HR, 0.91; 95% CI, 0.68-1.21) and White participants (HR, 0.97; 95% CI, 0.91-1.04) (*P* for interaction = .66) (Figure S4). The results remained consistent in the sensitivity analysis limited to trials reporting outcomes for both Black and White participants (Figure S5). Also, there was no significant effect of DPP-4 inhibitors on the risk of composite renal outcomes among Black participants (HR, 1.31; 95% CI, 0.80-2.14) and White participants (HR, 1.03; 95% CI, 0.86-1.24) (Figure S4).

The overall quality of evidence from our primary analysis was from moderate to high (Table 1) based on GRADE evalution. Evidence was downgraded because of, for example, statistical hetereogenity between trials and imprecision (such as only one trial included). The ICEMAN tool evaluation suggested a moderate credibility of our effect modification analyses (Text S1).

We performed a trial sequential analysis to test whether the sample size available for Black participants was deemed of sufficient power to reach reliable conclusions. Our trial sequential analysis suggested that the required information size needed to detect a 15% treatment benefit for MACE with DPP-4 inhibitors, GLP-1RAs, and SGLT2 inhibitors was 11 414, 17 495, and 14 950, respectively. Therefore, the current meta-analyses involving effects on MACE, including 1910, 3191, and 928 Black participants for DPP-4 inhibitors, GLP-1Ras, or SGLT2 inhibitors, respectively, had inadequate power to make reliable conclusions about treatment efficacy among Black participants (Figure S6). Regarding the composite endpoint of CV death/HHF, the required information size for SGLT2 inhibitors was 4583, indicating that the current evidence based on a sample size of 718 was inconclusive and further studies are required. Trial sequential analyses for other treatments and outcomes were infeasible because of the limited number of studies included.

4 | CONCLUSIONS

Although Black participants account for 11.7% of the diabetes population in the United States,[8] participation of Black patients in clinical trials that evaluated novel glucose-lowering agents from 2013 to 2021 was less than 5% of trial enrollees. In this meta-analysis of CV and renal outcome trials, SGLT2 inhibitors were associated with a decreased risk of MACE, the composite endpoint of CV death/HHF, and composite renal outcomes in White patients with or without T2D and GLP-1RAs reduced the risk of MACE. However, although point estimates tended to be similar, neither of these novel glucose-lowering agents was significantly associated with a reduction in the risk of the same cardiorenal outcomes in Black participants. The overall quality of evidence was judged as moderate or high. Importantly, our trial sequential analysis suggests that the sample size available provided inadequate statistical power to detect a significant treatment effect for CV outcomes in Black participants. Thus, whether CV or renal benefits of SGLT2 inhibitors or GLP-1RAs are generalizable to the Black population remains unknown because of the limited representation of such individuals in major clinical trials showing these agents' cardiorenal benefits.

Diabetes causes more than 900 American deaths daily, with over two-thirds attributed to CV disease. Glucose control can decrease the CV risk moderately at best. Evidence suggests that GLP-1RAs and SGLT2 inhibitors have created unprecedented opportunities for improving CV outcomes in individuals with T2D. Furthermore, the U.S. Food and Drug Administration has authorized the use of SGLT2 inhibitors to improve cardiorenal outcomes in non-diabetic patients with reduced ejection fraction heart failure and non-diabetic patients with chronic kidney disease. However, the current meta-analysis showed that Black individuals were under-represented in the key clinical trials showing the cardiorenal benefits of these new therapies, the result being that the generalizability of these trials to this racial subgroup remains unknown. Sample sizes would have to be 5-16 times larger than currently available to provide sufficient power to detect a 15% relative risk reduction in the risk of CV outcomes.

Mishriky et al. reported a meta-analysis of 11 clinical trials for GLP-1RAs and SGLT2 inhibitors published by November 2018 and

found a non-significant association of these new agents with CV outcomes.[3] However, their study only examined the MACE outcome in Black participants and did not test the interaction of race and treatment or conduct power analysis. Our analysis expands to the most updated cumulative evidence through March 2021 including 22 clinical trials, and importantly, performs a comprehensive evaluation of three clinical outcomes, including MACE, CV death/HHF, and composite renal outcomes. Moreover, our study is an important contribution to the existing literature because it shows that the sample size available was insufficient for conclusive evidence in support of treatment recommendations for Blacks.

Individuals experiencing social disadvantages face barriers to clinical research participation. Long geographic distance to treatment, lack of transportation, and lower income also disproportionately affect racial and ethnic minority groups and can be associated with low enrolment in clinical trials.[10] Promoting enrolment of under-represented racial and ethnic minority groups in clinical trials is particularly relevant for antidiabetic agents because Black individuals face a disproportionately high burden of diabetes and CV disease. Addressing disparities in clinical trial enrolment can improve health equity by understanding how the clinical and social characteristics of these patients impact accessibility to novel therapies and the associated outcomes.

The absence of patient groups that have been historically marginalized precludes understanding how critical social determinants, for example, income, educational attainment, and neighbourhood-level characteristics, may influence access and response to contemporary therapies. Race and ethnicity are social constructs, and social determinants of health are underlying, contributing factors of inequities across racial and ethnic groups. Studies have shown that social and structural factors (e.g. socioeconomic status and built environment) contribute to variation in CV disease and diabetes outcomes, therapy access, and adherence.[11-13] The absence of diversity in clinical study participation may sustain health inequities by failing to account for social and structural factors in the investigation of novel therapies and can have negative consequences for patients in the real world.

The current study is subject to limitations. First, this is a meta-analysis of the results from stratified analyses that are not randomized. It is more probable that there were differences in baseline risk or selection bias within strata. Second, only two clinical trials have reported subgroup analyses among Hispanic participants, thus precluding a meta-analysis of this patient group. Finally, there was moderate statistical heterogeneity across trials within the meta-analysis, indicating that different drugs within the same class may have different effects on CV outcomes in race and ethnic minority groups. Unfortunately, subgroup analyses of individual drugs could not be performed because of the limited number of trials included.

Point estimates for Black and White participants were similar for the evaluated drug classes and endpoints but confidence intervals for effect estimates among Blacks were large, rendering most results inconclusive. Individuals of Black race are under-represented in key clinical trials evaluating the CV endpoints of novel glucose-lowering agents. Despite efforts to eliminate healthcare disparities, our study highlights the persistent gap in adequate consideration of diverse patient groups in cardiorenal outcomes trials.

CONFLICT OF INTEREST

HT is a consultant at EvidPro, LLC. IH receives consulting fees from Pfizer, outside of the submitted work. The other authors declare no competing interests.

AUTHOR CONTRIBUTIONS

HT and JG conceptualized and designed the study. HT and WS selected the studies and extracted the data. HT performed the statistical analysis. All authors interpreted the data. HT drafted the manuscript, and all other authors critically reviewed the report. JG is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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