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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 enrollment

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Running title: Cardiorenal benefits of novel glucose-lowering agents

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BACKGROUND

Racial and ethnic diversity in clinical trials serves as a metric of societal equality and access to health care. Unfortunately, as in most large-scale studies of cardiovascular (CV) benefits/risks, the Black populations have been vastly underrepresented, 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 cotransporter-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 cardiorenal 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 health care [1]. This study intended to address an omnipresent failure in the chain of health equity: under-enrollment of socially disadvantaged populations in key clinical trials of potentially life-saving treatments and its negative consequences on the external validity, equality, and scientific rigor of research.

METHODS

PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched from inception up to March 28th, 2021

according to a predesigned search strategy (**Table S1**). Two reviewers (HT and WS) independently selected potential trials based on the following inclusion criteria: 1) CV and renal outcome trials designed to evaluate the effects of novel glucose-lowering agents on CV or renal outcomes; 2) trials investigating DPP-4 inhibitors, GLP-1RAs, and SGLT2 inhibitors; 3) trials reporting of MACE outcome, composite endpoint of CV death/heart failure hospitalization (HHF), or composite renal outcomes (including end-stage kidney disease, a sustained decline in the estimated GFR, death from renal or CV causes, or a doubling of the serum creatinine level) in explicit strata of Black or White adults (≥18 years) with or without T2D. The detailed definitions of these outcomes by each trial were 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) as compared to 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 ovariall 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 0.05. Statistical analyses were performed using STATA (Version 14; Stata Corp., College Station, TX) and TSA 0.9.5.10 beta (https://www.ctu.dk/tsa/downloads.aspx).

RESULTS

The structured literature search retrieved 9,648 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 (5 for DPP-4 inhibitors, 7 for GLP-1RAs, and 10 for SGLT2 inhibitors) (see references in the **Supplemental materials**) (**Figure S1)**. The 22 trials included a total of 175,893 participants, among whom 7,944 (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 in White populations[7]. The basic characteristics and definitions in CV and renal outcomes for each trial are presented in **Table S3 and Table S2**, respectively.

Four SGLT2 inhibitor outcome trials reported the outcome of MACE (3 for Black participants and 4 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 0.97. The composite endpoint of CV death/HHF was available in 6 trials (5 trials for Black participants and 6 trials for White participants) (**Figure 1**). SGLT2 inhibitors were associated with a decreased risk by 26% in Black participants (HR, 0.74; 95% CI, 0.53-1.04) and by 21% in White participants (HR, 0.79; 95%CI, 0.71-0.87). There was no significant difference in treatment effect between Black participants and White participants (p for interaction = 0.87). 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% (HR, 0.66; 95% CI, 0.57-0.78) (p for interaction = 0.82) (**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 0.77 (**Figure S3**).

MACE outcome was assessed in 5 DPP-4 inhibitors trials (5 trials for Black participants and 4 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 = 0.66) (**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 due to (e.g., statistical hetereogenity between trials) and imprecision (e.g., 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 1,910, 3,191, and 928 Black participants for DPP-4 inhibitors, GLP-1RAs, or SGLT2

inhibitors 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 4,583, 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 due to the limited number of studies included.

CONCLUSIONS

Although Black participants account for 11.7% of the diabetes population in the U.S.[8], participation of Black patients in clinical trials that evaluated novel glucose-lowering agents between 2013 and 2021 was < 5% of trial enrollees. In this meta-analysis of CV and renal outcometrials, 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 due to the limited representation of such individuals in major clinical trials demonstrating these agents' cardiorenal benefits.

Diabetes causes over 900 American deaths daily, with over two-thirds attributed to CV disease. Glucose control can decrease 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. FDA 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 present meta-analysis demonstrated that Black individuals were underrepresented in the key clinical trials demonstrating 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 throughout 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 demonstrates 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[9]. 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 enrollment in clinical trials[10]. Promotitng enrollment of underrepresented 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 enrollment can improve health equity by understanding how 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, e.g., income, educational attainment, neighborhood-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[9].

The present study is subject to limitations. First, this is a meta-analysis of the results from stratified analyses that are not randomized. It is more likely 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 due to 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, yielding most results inconclusive. Individuals of Black race are under-represented in key clinical trials evaluating CV endpoints of novel glucose-lowering agents. Despite efforts to eliminate health care disparities, our study highlights the persistent gap in adequate consideration of diverse patient groups in cardiorenal outcomes trials.

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None

CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

H.T and J.G. conceptualized and designed the study. H.T. and W.S. selected the studies and extracted the data. H.T. performed the statistical analysis. All authors interpreted the data. H.T. drafted the manuscript, and all other authors critically reviewed the report. J.G. 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.

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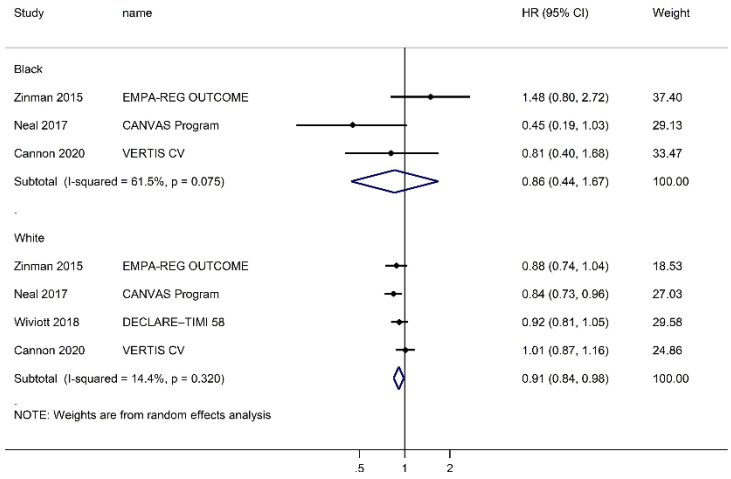
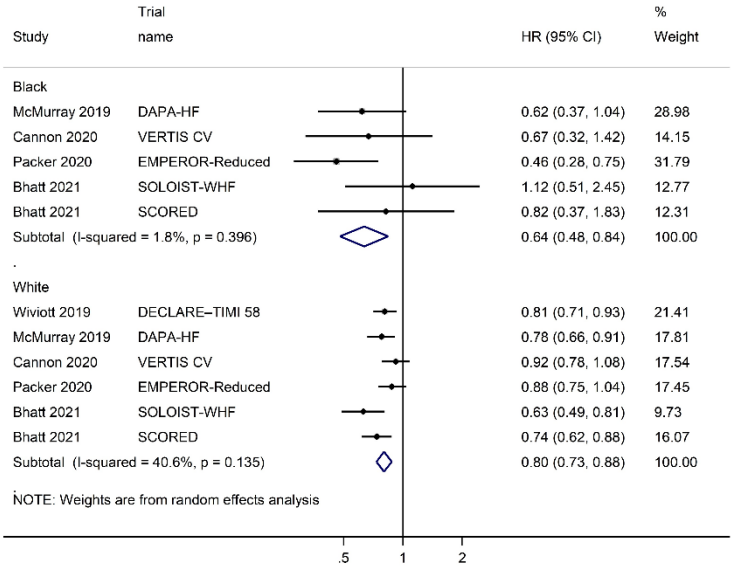
Figures

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

A. MACE outcome (p for interaction = 0.97)



B. Composite endpoint of cardiovascular death/heart failure hospitalization (p for interaction = 0.87)



C. Composite renal outcomes (p for interaction = 0.75)

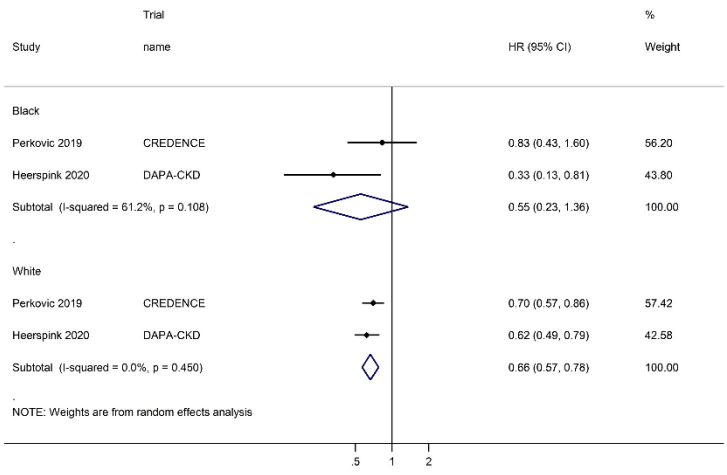


Table 1. GRADE summary of findings and certainty of the evidence

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)	1,132 (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)	5,221 (2 trials)	⨁⨁⨁⨁ **High**
GLP-1RAs			
MACE-Black	HR 0.92 (0.67 – 1.26)	3,191 (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)	1,910 (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)	5,596 (1 trial)	⨁⨁⨁◯ **Moderate**[b]

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

[a]Downgrade one level due to inconsistency (e.g., statistical hetereogenity between trials).

[b]Downgrade one level due to imprecision (e.g., only one trial included).

GRADE Working Group grades of evidence:

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.