

Cardiovascular Outcomes of Antidiabetes Medications by Race/Ethnicity: a systematic review and meta-analysis

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Abstract

Background: The consistency of cardiovascular risk reduction by antidiabetes medications across racial and ethnic groups remains unclear. The aim of this study was to analyze racial/ethnic patterns in the results of cardiovascular outcomes trials of antidiabetes medications in people with type 2 diabetes.

Method: PubMed and Cochrane library databases were searched from the inception dates to December 2019. Cardiovascular outcome trials in type 2 diabetes that randomized participants to active or control treatment and reported results by race/ethnic groups or region were included.

Results: A total of 16 studies were included in this meta-analysis. Among White participants, active antidiabetes medication, compared with control treatment, significantly decreased the composite cardiovascular outcomes (OR=0.90, 95% CI 0.86-0.94, $p<0.05$). Among Asian participants, active antidiabetes medication, compared with control treatment, also significantly decreased the composite cardiovascular outcomes (OR=0.82, 95%CI 0.76-0.90, $p<0.05$). Among Black participants (OR=0.96, 95% CI 0.69-1.32, $p=0.79$) and subjects from other groups (mostly Hispanics or Pacific Islanders) (OR=0.92, 95% CI 0.81-1.04, $p=0.16$), active anti-diabetes medication resulted in nominal but non-significant decreases in the composite cardiovascular outcomes, compared with the control treatment.

Conclusions: Antidiabetes drugs demonstrated cardiovascular safety in people with type 2 diabetes from all racial/ethnic groups studied, but achieved significant composite cardiovascular risk reduction only in White and Asian participants, perhaps due to differences in sample size and power.

Research In Context

Evidence before this study

Multiple cardiovascular outcomes trials (CVOTs) of antidiabetes medications have been completed and the results show variability among classes of glucose-lowering agents in their effects on cardiovascular events. The disparities of cardiovascular risk reduction by antidiabetes medications across racial and ethnic groups remains unclear.

Added value of this study

Antidiabetes medications demonstrated cardiovascular safety in people with type 2 diabetes from all racial/ethnic groups studied but achieved significant composite cardiovascular risk reduction only in White participants and Asian participants, but not in Black participants and subjects from other groups (mostly Hispanics or Pacific Islanders), perhaps due to differences in sample size and power.

Implications of all the available evidence

Significant cardiovascular benefits by the assessed antidiabetes medications were only confirmed in White and Asian population. Given the disproportionate burden of type 2 diabetes and its complications in African Americans, Latinos, Native Americans and other ethnic groups, it is imperative to demonstrate the efficacy of medications and interventions for cardiovascular risk reduction in these populations. The underrepresentation of Blacks and other high-risk groups in the populations enrolled in CVOTs opens the question as whether the benefits demonstrated for Whites and Asians in CVOTs can be also expected to apply to other groups.

Introduction

Racial and ethnic disparities in the risk factors, prevalence and complications of type 2 diabetes mellitus (T2DM) have been widely reported (1–5). For example, the National Health and Nutrition Examination Survey (NHANES) estimates show approximately 2-fold or higher prevalence of diagnosed T2DM in African Americans, Hispanic Americans, Asian Americans and American Indians, compared with non-Hispanic white Americans (1, 6, 7). Other reports have indicated that T2DM tends to develop at a younger age and lower body mass index in Asian compared with White or African populations (8, 9).

The quality of glycemic control and clinical consequences of the microvascular complications of diabetes, such as retinopathy, amputation, and kidney disease, have also been reported to show ethnic/racial disparities (4, 10, 11). The disparities in microvascular complications can be eliminated with equal access to care and optimal glycemic control (12, 13).

Unlike microvascular complications, which can be prevented by optimal glycemic control, the approach to the prevention of cardiovascular disease (CVD) requires targeting all modifiable cardiovascular risk factors along with glucose control (14, 15). Analysis of data from 1,344,899 patients in an insured population followed from 2002 to 2012 showed that Blacks, Latinos, and Asians had lower risk of coronary heart disease (CHD) across all risk categories, compared with Whites (16). However, despite having a lower prevalence of CHD and less atherogenic lipid profile, Blacks have a higher CHD mortality rate compared with Whites (17–19). The age-adjusted CHD death rates per 100 000 were 132.3 for non-Hispanic White men versus 146.5 for non-Hispanic Black men, and 67.9 for non-Hispanic White women versus 85.4 for non-Hispanic Black women (18).

Landmark randomized, controlled clinical trials of aggressive glycemic control failed to demonstrate reduction in CVD events in people with T2DM, during the active follow-up period (20–22). However, other more recent studies have tested specific antidiabetes medications (rather than glucose control, per se) for the pre-specified primary outcome of major adverse cardiovascular events (MACE). Several of these cardiovascular outcomes trials (CVOTs) of antidiabetes medications have been completed and the results show variability among classes of glucose-lowering agents in their effects on CVD events. Furthermore, enrollment of subjects into the CVOTs does not appear to reflect any attempt at ensuring racial/ethnic balance in the study populations. Consequently, the data from the individual CVOTs do not provide full insight into the efficacy of the study medications across racial/ethnic groups. Given the

potential for interplay among prevalent CVD risk factors, genetic background, socioeconomic factors, and other variables, in determining outcomes of the CVOTs in different racial/ethnic groups, we conducted a meta-analysis to explore consistency of results from CVOTs across race/ethnicity.

Methods

Data Sources and Searches

This study was conducted according to standard guidelines for conducting and reporting systematic reviews (PRISMA checklist). We searched PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) for randomized control trials (RCTs) from inception until December 2019.

Study Selection

The inclusion criteria were: (1) type 2 diabetes cardiovascular outcome trials; (2) prespecified cardiovascular events in the active treatment and control groups were reported by race/ethnicity or region of participants; (3) the incidence rates of prespecified cardiovascular events were reported by race/ethnicity or region of participants, so that it was possible to calculate the cardiovascular events from the rates and the total number of participants. The exclusion criteria were: (1) studies that were not RCTs; (2) non-cardiovascular outcome trials; (3) studies that enrolled participants with type 1 diabetes; (4) trials without report of subgroup analysis stratified by race; (5) trials that did not report MACE in subgroups stratified by race.

The search terms used for this meta-analysis were cardiovascular outcome trials; randomized controlled trials; type 2 diabetes; renal outcomes; placebo-controlled trials.

Data Extraction and Quality Assessment

We used standardized forms for data extraction. Two authors assessed search results independently and extracted data, focusing on year of journal publication; treatments and baseline demographic and clinical characteristics; and cardiovascular events, stratified by race or region. Based on the available information on race/ethnicity or regions in the selected trials, we stratified participants into four groups: White (Caucasian), Asian, Black (African, African-American), and other participants (comprised mostly of Hispanics and Pacific Islanders). Quality assessment was made by using the Cochrane risk of bias tool. We addressed discrepancies by inviting a third author to join the discussion, and resolved disagreements by consensus.

Data Synthesis and Analysis

In each pre-specified race or region, results were reported by using the pooled odds ratio (OR) along with the 95% confidence interval (95% CI) of the composite cardiovascular events between the active anti-diabetes agent group and the control group (including placebo control and active agent control).

Statistical heterogeneity between trials was assessed by I^2 statistic. Fixed-effects models or random-effects models were used according to the level of heterogeneity. Funnel plot was used to examine the

publication bias. We performed sensitivity analyses, based on placebo use in the control group; restriction of cardiovascular outcomes to MACE; or the type of antidiabetic medication used in the active treatment groups. Statistical analyses were performed with Review Manager statistical software package (Version 5.3, Nordic Cochrane Center, Copenhagen, Denmark).

Results

Included studies

Through the search, we identified 678 records. As Fig. 1 showed, finally 16 studies were included in the quantitative synthesis. Of the included studies, 14 were placebo-controlled and 2 studies compared the test medications against active agents (**Table S1**). The primary outcomes of 14 placebo-controlled studies were MACE; of the other two studies, the primary outcome was hospitalization for heart failure in one and renal events in the other. The antidiabetes medications utilized in the trials included glucagon-like peptide-1 receptor analog (GLP-1RA) in 6 studies, sodium glucose cotransporter 2 inhibitors (SGLT2i) in 4 studies, and dipeptidyl-peptidase-4 (DPP-4) inhibitors in 3 studies. We included one study each that tested basal insulin, a peroxisome proliferation activated receptor (PPAR)- γ agonist, or an alpha glucosidase inhibitors (AGI) (**Table S1**).

Some notable CVOTs could not be added to our list of selected studies because they lacked data on racial/ethnic breakdown of pertinent outcomes in treatment vs. control arms. The latter included ELIXA (23), CANVAS (24), ORIGIN (25), PROactive (26) and omarigliptin cardiovascular safety trial (27).

Quality assessment

The studies all utilized a randomized, placebo- or active-controlled, double-blind, parallel treatment design. The eligibility criteria were clearly described, as were baseline characteristics in participants in the comparison groups. Overall, the risks of bias were evaluated low in most of the trials (**Table S2**). The visual inspection of the funnel plots indicated an even distribution of the variables (**Figure S1-3**).

Risk of composite cardiovascular outcomes stratified by race/ethnicity

Based on the reported event rates by race/ethnicity in the active arm and the placebo/control arm of the studies included in the present meta-analysis, there were no significant differences in the overall rates of composite cardiovascular outcomes across racial/ethnic groups (Fig. 2A-2D). However, when comparing the effects of treatment vs. control, we observed significant racial/ethnic disparities in cardiovascular outcomes of antidiabetes medication.

Among White participants, active antidiabetes medications, compared with control treatment, significantly decreased the composite cardiovascular outcomes (OR = 0.90, 95% CI 0.86–0.94, $p < 0.05$) (Fig. 2A). Among Asian participants, active antidiabetes medications, compared with control treatment, also significantly decreased the composite cardiovascular outcomes (OR = 0.82, 95%CI 0.76–0.90, $p <$

0.05) (Fig. 2B). However, among Black participants, active antidiabetes medications, compared with control treatment, did not significantly decrease the composite cardiovascular outcomes (OR = 0.96, 95%CI 0.69–1.32, $p = 0.79$) (Fig. 2C). A similar pattern was found when analyzing the effects of antidiabetes medications vs. control treatment in other racial/ethnic groups comprising mostly Hispanics and Pacific Islanders (OR = 0.92, 95%CI 0.81–1.04, $p = 0.16$) (Fig. 2D). In further exploration, we combined Blacks and other groups to constitute a third block of non-White, non-Asian participants and repeated our calculations. The results in this expanded population still did not show significant reduction of composite cardiovascular outcomes in Blacks and other groups (OR 0.94; 95% CI 0.85–1.04) (Table 1).

Table 1

Primary Outcomes of CVOTs Stratified by Race/Ethnicity, Combining Blacks and Other Groups*

Race/Ethnic groups	Number of participants (Active/Control)	Proportions (%)	Odds ratio	95%CI	I ²
Total					
White	40396/40209	67.15	0.90	0.86–0.94	41%
Asian	11050/10643	18.07	0.82	0.76–0.90	46%
Black/Others	8862/8871	14.78	0.94	0.85–1.04	47%
Primary outcomes of CVOTs in placebo-controlled trials					
White	35288/35135	65.96	0.89	0.85–0.93	46%
Asian	10202/9781	18.72	0.83	0.76–0.91	44%
Black/Others	8169/8187	15.32	0.96	0.86–1.06	47%
Primary outcome restricted to MACE					
White	37247/27094	63.77	0.92	0.88–0.96	8%
Asian	10073/9627	19.53	0.86	0.78–0.94	41%
Black/Others	8413/8432	16.70	0.94	0.80–1.11	51%
Primary outcome in treatment with GLP-1RA					
White	18203/18239	72.98	0.88	0.82–0.94	34%
Asian	2101/2130	8.47	0.66	0.53–0.82	0%
Black/Others	4637/4621	18.54	0.88	0.77–1.01	22%
Primary outcome in treatment with DPP4 inhibitor					
White	7010/6902	66.87	0.97	0.88–1.07	0%
Asian	1342/1369	13.03	1.03	0.80–1.31	0%
Black/Others	2067/2115	20.10	1.30	1.07–1.58	0%
Primary outcome in treatment with SGLT2 inhibitor					
White	9992/9925	70.18	0.84	0.77–0.91	71%
Asian	3076/2620	20.07	0.72	0.60–0.85	30%
Black/Others	1395/1370	9.75	0.79	0.61–1.03	0%
Primary outcome in treatment with basal insulin					
*Hispanics, Pacific Islanders, Hawaiian, American Indian, Alaska Native					

Race/Ethnic groups	Number of participants (Active/Control)	Proportions (%)	Odds ratio	95%CI	I ²
White	2891/2882	79.51	0.96	0.80–1.14	/
Asian	317/332	8.94	0.42	0.21–0.81	/
Black/Others	432/407	11.55	0.56	0.34–0.95	/
Primary outcome in treatment with PPAR antagonist					
White	2300/2259	63.92	1.03	0.85–1.25	/
Asian	942/942	26.42	0.72	0.50–1.03	/
Black/Others	331/358	9.66	0.87	0.53–1.43	/
Primary outcome in treatment with AGI					
White	/	0	/	/	/
Asian	3272/3250	100	0.97	0.85–1.11	/
Black/Others	/	0	/	/	/
<i>*Hispanics, Pacific Islanders, Hawaiian, American Indian, Alaska Native</i>					

Sensitivity analyses

We performed sensitivity analyses based on assessment of only placebo-controlled studies, restriction of outcomes to MACE, and type of antidiabetes medication. Evaluation of only the placebo-controlled trials did not change our main findings: the reduction in composite cardiovascular outcomes was significant in White and Asian patients, but not in Blacks or other groups (**Table S3 and Figure S4-S7**).

The overall pattern observed for the primary outcomes was recapitulated when analysis was restricted to MACE without considering other outcomes. Significant reductions in MACE occurred in White and Asian patients, but not in Black patients or participants from other racial/ethnic groups (**Table S3 and Figure S8-S11**).

There appeared to be racial/ethnic differences in the cardiovascular effects of certain medications. CVOTs that utilized GLP-1RA as treatment demonstrated significant decrease of the composite cardiovascular outcomes in both White and Asian patients, but not in Blacks or other groups (**Table S3 and Fig. 2A-2D**). When compared with the control group, treatment with SGLT2 inhibitors resulted in point estimates for risk reduction that were nominally greater in Asians (OR 0.72) and Blacks (OR 0.73) compared with Whites (OR 0.84) and other groups (OR 0.82). However, owing to wide confidence intervals, the effects were significant only in White and Asian patients (**Table S3 and Fig. 2A-2D**). With DPP-4 inhibitors, there was a neutral effect in Whites and an apparent trend toward increased composite

cardiovascular outcomes in non-White groups that reached statistical significance in Black patients (OR = 1.36, 95%CI 1.04–1.77, $p < 0.05$) (**Table S3 and Fig. 2A-2D**).

The only trial of basal insulin included in the present meta-analysis compared degludec treatment with an active control agent (glargine), and reported a significant reduction in composite cardiovascular outcomes in both Black patients (OR 0.29; 95% CI 0.11–0.75) and Asian patients (OR 0.42; 95% CI 0.21–0.81), but not in White or in other groups (**Table S3 and Fig. 2A-2D**). There was incomplete racial/ethnic information regarding cardiovascular outcomes of treatment with PPAR- γ antagonist and AGI, but their effects were generally neutral in the populations studied (**Table S3 and Fig. 2A-2D**).

Discussion

Our meta-analysis of 16 RCTs of antidiabetes medications that pre-specified cardiovascular outcomes and provided adequate pertinent data showed that the overall event rates did not differ significantly among participants from the different racial/ethnic groups. The latter finding probably reflects the inclusion criteria that targeted high-risk patients with type 2 diabetes for enrollment in the CVOTs.

However, when comparing the effects of antidiabetes medication versus placebo- or active-control treatment by racial/ethnic group, we did observe disparities in the magnitude and significance of cardiovascular risk reduction. In general, a significant reduction in the composite cardiovascular outcomes was achieved in Asian and White participants, but not in Blacks and other racial/ethnic groups (including Hispanics and Pacific Islanders).

Sensitivity analyses showed consistency of our main findings of racial/ethnic disparities in cardiovascular risk reduction across the two antidiabetes medication classes (GLP1-RA and SGLT2 inhibitors) that have demonstrated superiority over placebo in CVOTs. However, the findings regarding other agents that have not been reported to decrease cardiovascular risk (DPP-4 inhibitors, PPAR- γ agonist, basal insulin) were discordant. We observed a neutral effect of PPAR- γ agonist on composite cardiovascular outcomes, without racial/ethnic disparities; a neutral effect in Whites and Asians, but an apparent increased risk among Blacks and other groups in trials of DPP-4 inhibitors; and a neutral effect in Whites, but significantly decreased risk in Asians, Blacks and other groups in the trial of basal insulin. Thus, our overall meta-analysis results were strongly influenced by data from the studies that tested the effects of GLP1-RA and SGLT2 inhibitors on cardiovascular outcomes.

Given that the individual studies in our meta-analysis were powered for the overall enrolled population, not racial sub-groups, our present findings of disparities in cardiovascular outcomes must be taken with caution. Nonetheless, the consistent pattern of lack of significant reduction in cardiovascular outcomes with antidiabetes medications among Blacks and other non-White, non-Asian participants enrolled in the CVOTs is striking. The reduction of cardiovascular events requires interventions to control several co-morbid risk factors beyond glycemia. Optimal control of hypertension, dyslipidemia, inflammation, albuminuria; effective counseling regarding smoking cessation, are all components of a comprehensive strategy for maintaining good cardiovascular health (14, 15, 18).

The CVOTs included in the present meta-analysis generally focused on executing a specific study protocol, leaving the management of the numerous co-morbid risk factors to the discretion of community health care providers. Thus, it is plausible that heterogeneity in access to care and quality of control of co-morbid risk factors could have contributed to our findings of racial/ethnic disparities in the reduction of composite cardiovascular outcomes (9–11, 16, 28, 29). Indeed, there is ample documentation of the unevenness of cardiovascular risk factors across demographic groups; notably, higher rates of hypertension, albuminuria, and chronic kidney disease have been reported in Black, Latino and Native American populations compared with Whites (18, 30). The combination of diabetes and kidney disease increases the risk of cardiovascular mortality 3-fold compared with diabetes without kidney disease (31).

Although the overall rates of cardiovascular outcomes were similar among participants from various racial/ethnic groups in the CVOTs, perhaps reflecting the inclusion criteria that targeted high-risk patients with type 2 diabetes, the failure to demonstrate consistent risk reduction across groups requires further scrutiny. Studies that enrolled multi-ethnic participants have shown that, with equal access to care and equal treatment, disparities in clinical outcomes (including mortality) can be ameliorated (12, 13, 29, 32, 33).

Like all meta-analyses, the present study has some limitations. The capture of cardiovascular events by race/ethnicity was incomplete, as several notable CVOTs (23–27) did not report a breakdown of MACE by race/ethnicity in the treatment and control groups. Thus, despite our best efforts to be comprehensive and inclusive, the lack of publicly available data on pertinent racial/ethnic results forced us to rely mainly on CVOTs that used GLP-1RAs, DPP-4 inhibitors, SGLT2 inhibitors and basal insulin, which introduces possible selection bias. Also, although the level of heterogeneity across studies was low in this meta-analysis, data from separate studies with varied baseline characteristics, treatment regimen, and duration of follow-up were combined for analysis. Thus, our results should be interpreted with caution. Furthermore, the studies we examined seldom provided detailed information on baseline cardiovascular risk factors by race/ethnicity, which precluded further meta-regression analysis of possible explanatory variables related to our finding of disparities in cardiovascular outcomes.

Finally, and most importantly, the sample from Black and other racial/ethnic groups (Hispanics, Native Americans, Native Hawaiians, Pacific Islanders and residents of Oceania, Latin America and the Caribbean) was relatively small, which might have lowered statistical power to detect differences. Data from the U.S. Census Bureau indicate that, of the estimated 326 million total population, 60.6% self-identified as non-Hispanic Whites, compared with 18.3% Hispanics, 12.3% non-Hispanic Blacks, 5.6% Asians and 0.9% American Indians (34). The United Nations estimates that there are 1.34 billion people living in Africa (17.2% of the world's population (35)). Thus, the proportion of Blacks (4.3%) in our total meta-analysis population of 120,031 participants enrolled in the CVOTs indicates a marked under-representation of the Black population in the U.S. or globally. The enrollment of Hispanics in the CVOTs (< 10%) also is low relative to the 18.3% Hispanic representation in the U.S. population, but fairly comparable to the Latin America and the Caribbean representation (8.3%) in the global population (35).

In conclusion, the present meta-analysis shows that the aggregate point estimates and confidence intervals for the numerous agents that have been tested in CVOTs reached statistical significance for reduction of composite cardiovascular outcomes only in White and Asian participants, who together represented 85.2% of the 120,031 participants enrolled in those trials. For Blacks and other racial/ethnic groups (who together represented 14.8% of the enrollment), the meta-analysis showed general cardiovascular safety but not significant reduction in composite cardiovascular outcomes by the medications tested in the CVOTs. Given the disproportionate burden of type 2 diabetes and its complications in African Americans, Latinos, Native Americans and other ethnic groups, it is imperative to demonstrate the efficacy of medications and interventions for cardiovascular risk reduction in these populations. The suboptimal representation of Blacks and other high-risk groups in the populations enrolled in CVOTs leaves open the question as to whether the benefits demonstrated for Whites and Asians in these studies can be expected to apply to other groups. Clearly, adequately powered studies are required to answer this important public health question.

Declarations

Ethics approval and consent to participate

No applicable.

Consent for publication

No applicable.

Availability of data and materials

Data of all the clinical trials included in this meta-analysis could be reached from the published manuscripts.

Competing interests

Linong Ji has received fees for lecture presentations and consulting fees from AstraZeneca, Merck, Novartis, Novo Nordisk, Lilly, Roche, Sanofi-Aventis and Takeda, and grants/research support from AstraZeneca, Merck, Novartis, Novo Nordisk and Sanofi-Aventis; S.D.-J. has led clinical trials for AstraZeneca, Novo Nordisk, Inc., and Boehringer Ingelheim; has received consulting fees from AstraZeneca, Boehringer Ingelheim, Janssen, Merck & Co. Inc., and Sanofi; and has equity interests in Jana Care, Inc. and Aerami Therapeutics; no other relationships or activities that could appear to have influenced the submitted work.

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Authors' contributions

LJ and XC conceived and designed the study. XC and CL assisted with the methods. XC, CL and WY did the data analysis. XC and LJ drafted the initial manuscript. SD-J discussed study concept, reviewed and revised manuscript. All authors assisted with interpretation, commented on drafts of the manuscript, and approved the final version. LJ is the guarantor and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Abbreviations

AGI, alpha glucosidase inhibitor; CENTRAL, the Cochrane Central Register of Controlled Trials; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DPP-4, dipeptidyl-peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor analog; MACE, major adverse cardiovascular events; NHANES, National Health and Nutrition Examination Survey; OR, odd ratio; PPAR, peroxisome proliferation activated receptor; RCT, randomized control trial; SGLT2i, sodium glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus.

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Figures

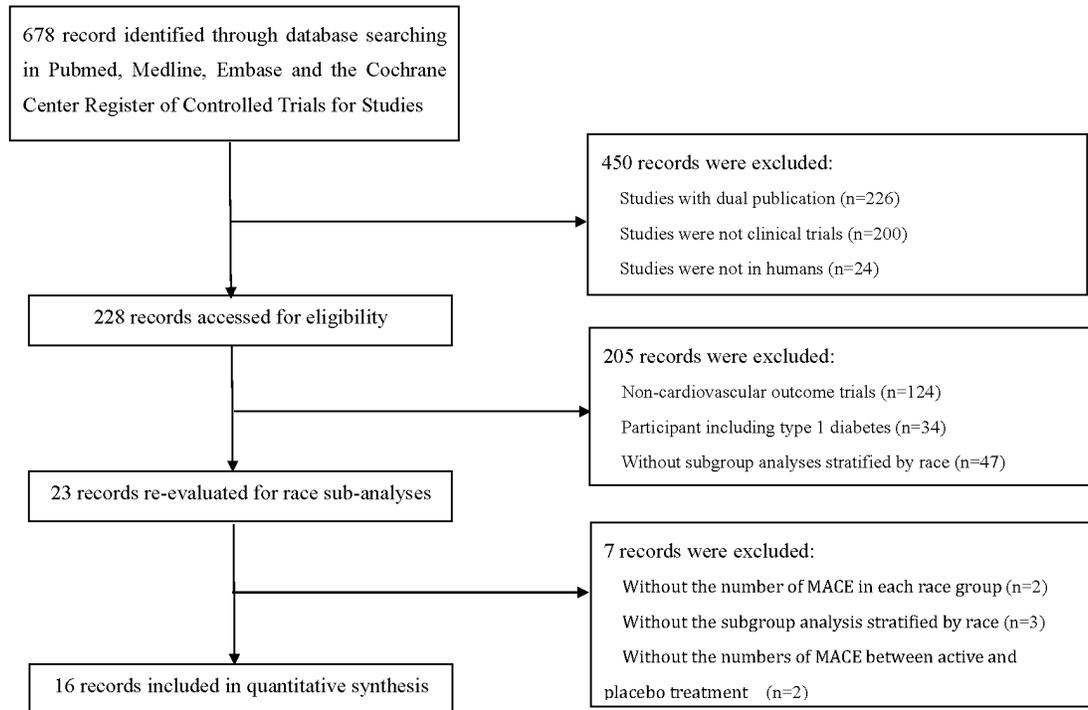
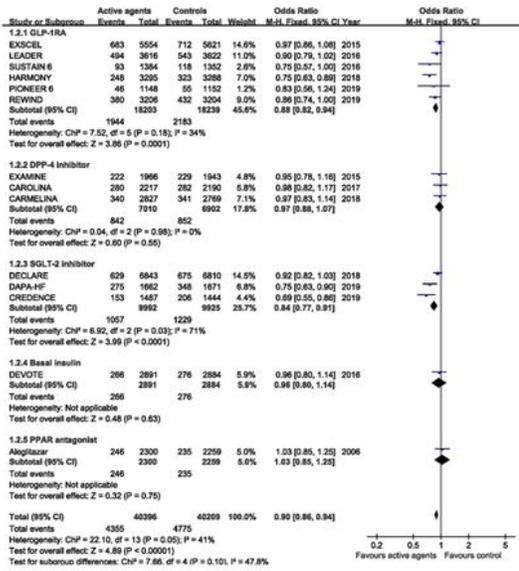


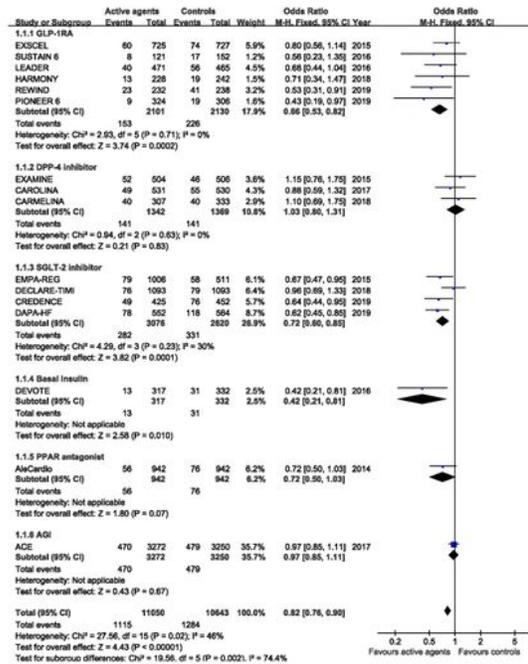
Figure 1

Flowchart of search results

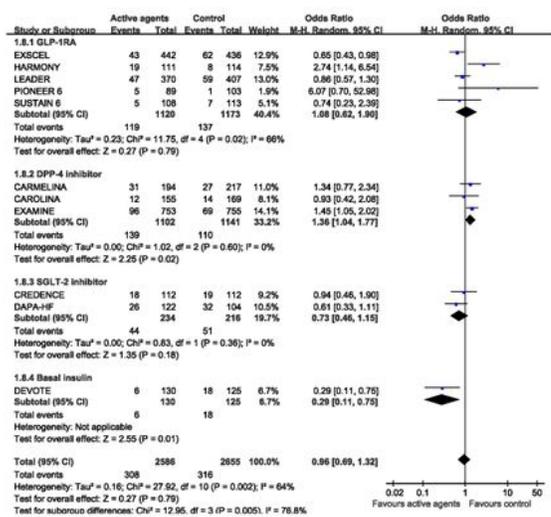
A



B



C



D

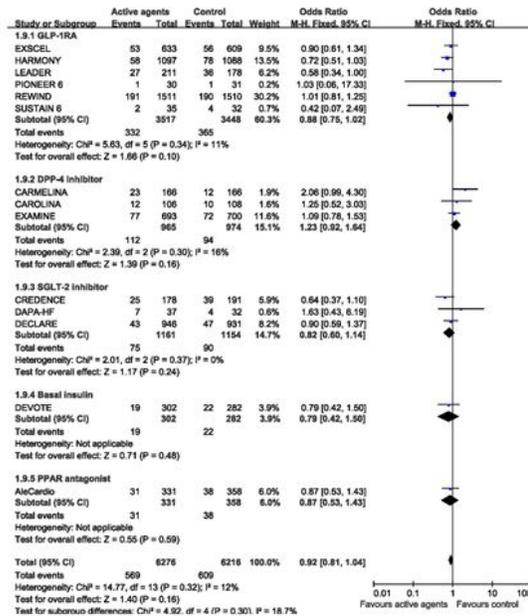


Figure 2

Primary outcomes of CVOTs in White patients, Asian patients, black patients and patients with type 2 diabetes from other racial/ethnic groups* Figure 2A: Primary outcomes of CVOTs in White patients with type 2 diabetes; Figure 2B: Primary outcomes of CVOTs in Asian patients with type 2 diabetes; Figure 2C: Primary outcomes of CVOTs in black patients with type 2 diabetes; Figure 2D: Primary outcomes of

CVOTs in patients with type 2 diabetes from other racial/ethnic groups* *Hispanics, Pacific Islanders, Hawaiian, American Indian, Alaska Native

Supplementary Files

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