Efficacy of Modern Diabetes Treatments DPP-4i, SGLT-2i, and GLP-1RA in White and Asian Patients With Diabetes: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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META-ANALYSIS

BACKGROUND

The pathophysiology of type 2 diabetes differs markedly by ethnicity.

PURPOSE

A systematic review and meta-analysis was conducted to assess the impact of ethnicity on the glucose-lowering efficacy of the newer oral agents, sodium–glucose cotransporter 2 inhibitors (SGLT-2i), glucagon-like peptide 1 receptor agonists (GLP-1RA), and dipeptidyl peptidase 4 inhibitors (DPP-4i), using evidence from randomized clinical trials (RCTs).

DATA SOURCES

A literature search was conducted in PubMed of all randomized, placebo-controlled trials of DPP-4i, SGLT-2i, and GLP-1RA. The search strategy was developed based on Medical Subject Headings (MeSH) terms and keywords.

STUDY SELECTION

A total of 64 studies that qualified for meta-analysis after full-text review based on predefined inclusion and exclusion criteria—RCTs with at least 50 patients in each arm, >70% of population from Asian or white group, duration ≥24 weeks, and publication up to March 2019—were selected for systematic review and meta-analysis.

DATA EXTRACTION

Data extraction was done for aggregated study-level data by two independent researchers. Absolute changes in HbA_{1c} (%) from baseline to 24 weeks between the drug and placebo were considered as the primary end point of the study.

DATA SYNTHESIS

Change in HbA_{1c} was evaluated by computing mean differences and 95% CIs between treatment and placebo arms.

LIMITATIONS

The study is based on summarized data and could not be separated based on East Asians and South Asians.

CONCLUSIONS

The glucose-lowering efficacy of SGLT-2i, and to a lesser extent DPP-4i, was greater in studies of predominantly Asian ethnicity compared with studies of predominantly white ethnicity. There was no difference seen by ethnicity for GLP-1RA.

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Type 2 diabetes presents a global threat to health. According to the International Diabetes Federation 2017 report, China has the highest number of people (114.4 million) with diabetes in the age-group 20–79 years. This is closely followed by India (72.9 million), which is projected to have the highest number of people with diabetes by 2045 (134.3 million) (1). Yet, most studies of diabetes are undertaken in Western populations (2), and treatment guidelines do not take ethnicity into account. The latest consensus report by the American Diabetes Association and the European Association for the Study of Diabetes recommends the use of relatively newer drugs such as sodium–glucose cotransporter 2 inhibitors (SGLT-2i), glucagon-like peptide 1 receptor agonists (GLP-1RA), and dipeptidyl peptidase 4 inhibitors (DPP-4i) in combination with metformin and lifestyle adjustments (3), unless cost is an issue. Nearly one-half of subjects with diabetes fail to achieve the recommended treatment target, and the reasons for this are multifactorial (4,5).

The pathophysiology and metabolic phenotype of type 2 diabetes differ markedly by ethnicity. For example, Southeast Asians and South Asians develop type 2 diabetes at younger age and lower BMI than whites (6–8), and β-cell deficiency has been reported to be a feature of Asian diabetes (6). These pathophysiological differences may impact on treatment efficacy, as most diabetes therapies largely target the underlying pathophysiological defects.

Even though a large number of studies have been carried out to measure safety and efficacy of antidiabetes agents, only a few report on these measures in those of different ethnicity. Previous meta-analysis on DPP-4i (reported in 2013) and GLP-1RAs (reported in 2014) based on ethnicity have reported that Asians responded better than non-Asians (9–11). These studies defined a population as Asian if it was >50% Asian and white if the population was <50% Asian and included studies of short duration. There are no previous studies reporting efficacy of SGLT-2 inhibitors based on ethnicity. Thus, we performed a systematic review and meta-analysis to comprehensively assess the impact of ethnicity on the glucose-lowering efficacy of relatively newer antidiabetes agents—SGLT-2i, GLP-1RA, and DPP-4i—using published evidence from randomized clinical trials (RCTs) reported up to 31 March 2019.

METHODS

Participants of three groups were considered for the study: *1*) those receiving DPP-4i alone or in combination with other drugs, *2*) those receiving SGLT-2i alone or in combination with other drugs, and *3*) those receiving GLP-1RA alone or in combination with other drugs.

Data Sources and Searches

The meta-analysis was carried out using methods proposed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (12). A literature search was conducted in PubMed for studies published up to 31 March 2019 by two independent investigators (S.G. and A.Y.D.) of all randomized, placebo-controlled trials of DPP-4i, SGLT-2i, and GLP-1RA. The search strategy was developed based on Medical Subject Headings (MeSH) terms and keywords. The search algorithm is presented in detail in Supplementary Material.

Study Selection

A title-based search was conducted followed by abstract screening. A full paper search of potentially eligible studies was also performed based on the predefined inclusion and exclusion criteria. Any discrepancies in selection were resolved by a third researcher (E.R.P.).

Inclusion Criteria

1. RCT on adult, nonpregnant participants aged ≥18 years with type 2 diabetes.
2. The efficacy of the drug was the primary outcome of the study.
3. Study reported the effect of drug versus placebo on HbA_{1c} in participants who were either drug naïve or on background therapy.
4. Study reported outcome by ethnicity, and one ethnic group constituted at least 70% or more participants.
5. Studies were filtered on the basis of human subjects, clinical trials, and age >19 years.
6. Study written in English.

Exclusion Criteria

1. Study duration was <24 weeks or >52 weeks.
2. The study had <50 participants in each study arm.
3. Participants were on insulin as background therapy.
4. Studies that were extensions of previous RCTs.
5. Studies that included participants in inpatient care.
6. Non-RCT studies and reviews.

Data Extraction

Data extraction was done for aggregated study-level data by two independent researchers. Absolute changes in HbA_{1c} (%) from baseline to 24 weeks between the drug and placebo were considered as the primary end point of the study. If data were not available for 24 weeks, 52 weeks was considered. Studies with duration >52 weeks were excluded, as these were open-label extensions. A standardized prepiloted form was used to extract data from the included studies for assessment of study quality and synthesis. Extracted information included author, year of publication, sample sizes, participant demographics and baseline characteristics, interventions, and HbA_{1c} outcomes of the lowest dose (in case multiple doses were reported and placebo). Further, the studies were classified by ethnicities provided in terms of whether percentage of participants in a particular ethnic group was >70%. A hierarchical approach was adopted to decide the relevance of studies based on title, abstract, and full manuscript. If a study had more than two relevant arms, each arm was treated separately. Selection process of relevant studies retrieved from databases was shown in a PRISMA-compliant flowchart.

We have used the classification of "Asian" or "white" of each study as it was reported in the manuscript. Where studies were conducted in relatively homogenous populations in Asian countries (e.g., Korea, China, Japan, and Taiwan), we have considered the participants to be in the "Asian" group. We have also followed the definitions of "East Asians" (China, Japan, Mongolia, North Korea, and South Korea) and "South Asians" (Afghanistan, Bangladesh, Bhutan, India, Maldives, Mauritius, Nepal, Pakistan, and Sri Lanka) from previous reports (13,14).

To ensure more robust ethnicity-specific outcomes, we required >70% of the population to be Asian or white for the study to be allocated to that ethnic group, and to ensure more robust treatment effects we limited our studies to

those where the study duration was ≥24 weeks and where there were >50 participants in the intervention and comparison arms.

Quality Assessment

The quality of eligible studies was evaluated by two independent researchers using the Cochrane Collaboration's risk-of-bias tool (15) for assessing the design, execution, and reporting of the included RCTs. Risk of bias was assessed in random-sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). The risk of bias was classified as high, low, or unclear. Funnel plot and Egger test were carried out to assess the publication bias of the overall studies for each drug.

Data Synthesis and Analysis

For each drug group, a meta-analysis was performed with the combined data and stratified analysis by ethnic group using the meta package in RStudio (version 1.0.153). Change in HbA_{1c} was evaluated by computing mean differences (MDs) and 95% CIs between treatment and placebo arms. The MDs were calculated as the change from baseline to end point. When SD was not reported, it was estimated by the formula provided by the Cochrane Handbook for Systematic Reviews of Interventions (16). Forest plots for white- and Asian-dominant groups were constructed using RStudio. Higgins I^2 statistic was used to evaluate between study heterogeneity and classified as low (<25%), moderate (25–75%), or high (>75%) (16). The Q statistic was used as a test of heterogeneity. τ^2 was estimated by the DerSimonian-Laird estimation method (17). A random effects model was used to estimate the pooled effect. Statistical significance was considered as P value <0.05. Tests for subgroup differences were carried out to check whether there were any significant differences between ethnic groups. Meta-regression analyses were performed to determine whether estimates of treatment effects were associated with prespecified clinical characteristics such as age, duration of disease, percentage of specific ethnic group, percentage of men, baseline BMI, and baseline HbA_{1c}. A sensitivity analysis was conducted considering study duration from 12 weeks to 52 weeks for all of the three drug groups, with all other criteria kept the same.

This review is registered with PROSPERO (CRD42019133587).

RESULTS

DPP-4i

Search Results and Study Characteristics

Initially, 1,411 articles were identified from the database, 12 articles were identified from references of other articles, and 26 articles were included in the meta-analysis. A total of 26 comparison pairs were retrieved, which satisfied the selection criteria (Supplementary Fig. 1*A*). The total number of study participants was 8,531, of whom 4,728 were randomized to treatment arms and 3,803 to the placebo arms. The white-dominant group (17 studies) consisted of 5,185 participants, of whom 3,051 participants were randomized in the treatment group and 2,134 participants in the placebo group. The Asian-dominant group (nine studies) consisted of 3,346 participants, of whom 1,677 participants were randomized in the treatment group and 1,669 participants in the placebo group (Fig. 1). The summary of included studies is shown in Supplementary Table 1.

Quality of Included Studies and Publication Bias Assessments

For the adequacy of sequence generation, 13 studies were categorized as unclear and 13 studies were categorized as low risk. All the included studies achieved the double blinding for the participants and the personnel. The allocation concealment was unclear in 16 studies, and 10 studies were at low risk. There was no particular indication of incomplete data, selective reporting, or other biases in any of the included studies (Supplementary Table 1*A* and Supplementary Fig. 1*B*). The Egger test and funnel plot suggested that there was no asymmetric pattern and no particular concern regarding publication bias (P = 0.626) (Supplementary Fig. 1*C* and *D*).

Efficacy Outcomes

HbA_{1c} data were pooled from the 26 comparison pairs from 26 studies. Overall, the difference between the treatment and placebo groups was −0.53 (95% CI −0.62, −0.44; I^2 = 78%) favoring treatment (Fig. 1). In the white-dominant group, the difference between treatment and placebo groups was −0.49 (95% CI −0.59, −0.38; I^2 = 74%) favoring treatment. In the Asian-dominant group, the difference between treatment and comparison groups was −0.62 (CI −0.80, −0.45; I^2 = 84%) favoring treatment (Fig. 1). The test for subgroup differences (random effects model) showed no difference (P = 0.1919) between the two groups (Supplementary Table 2*A*).

Exploratory Analysis

The median duration of diabetes was 6.1 years (range 2.9–12.2) in the white-dominant group and 6.4 years (0.97–8.15) for the Asian-dominant group. The median HbA_{1c} at baseline was 8.065% (7.8–8.6) in the white-dominant group and 8.5% (7.9–9.4) in the Asian-dominant group. The median BMI at baseline was 31.7 kg/m^2 (28.1–32.90) in the white-dominant group and 25.9 kg/m^2 (25.30–27.90) in the Asian-dominant group.

Meta-Regression

The univariate meta-regression analysis showed that age (P = 0.33), percentage participants who were white (P = 0.12), HbA_{1c} at baseline (P = 0.98), duration of diabetes (P = 0.22), percentage of participants who were men (P = 0.60), and BMI at baseline (P = 0.38) were not associated with the change in HbA_{1c} from baseline (Supplementary Table 3 and Supplementary Fig. 4).

Sensitivity Analysis

Here, we included additional studies with a shorter duration (from 12 weeks to 52 weeks). Out of the 1,411 articles identified from the database, an additional 7 studies were identified, totaling 33 studies included in the sensitivity analysis. Overall, the difference between the treatment group and comparison group was −0.59 (95% CI −0.70, −0.48; I^2 = 94%) favoring treatment (Supplementary Fig. 1*E*). In the white-dominant group, the difference between treatment group and comparison group was −0.49 (95% CI −0.59, −0.39; I^2 = 73%) favoring treatment. In the Asian-dominant group, the difference between treatment and comparison groups was −0.73 (95% CI −0.88, −0.57; I^2 = 94%) favoring treatment (Supplementary Fig. 1*E*). Testing for subgroup differences (random effects model) showed a greater response in the Asians compared with the white-predominant group (P = 0.0098) (Supplementary Table 2*B*).

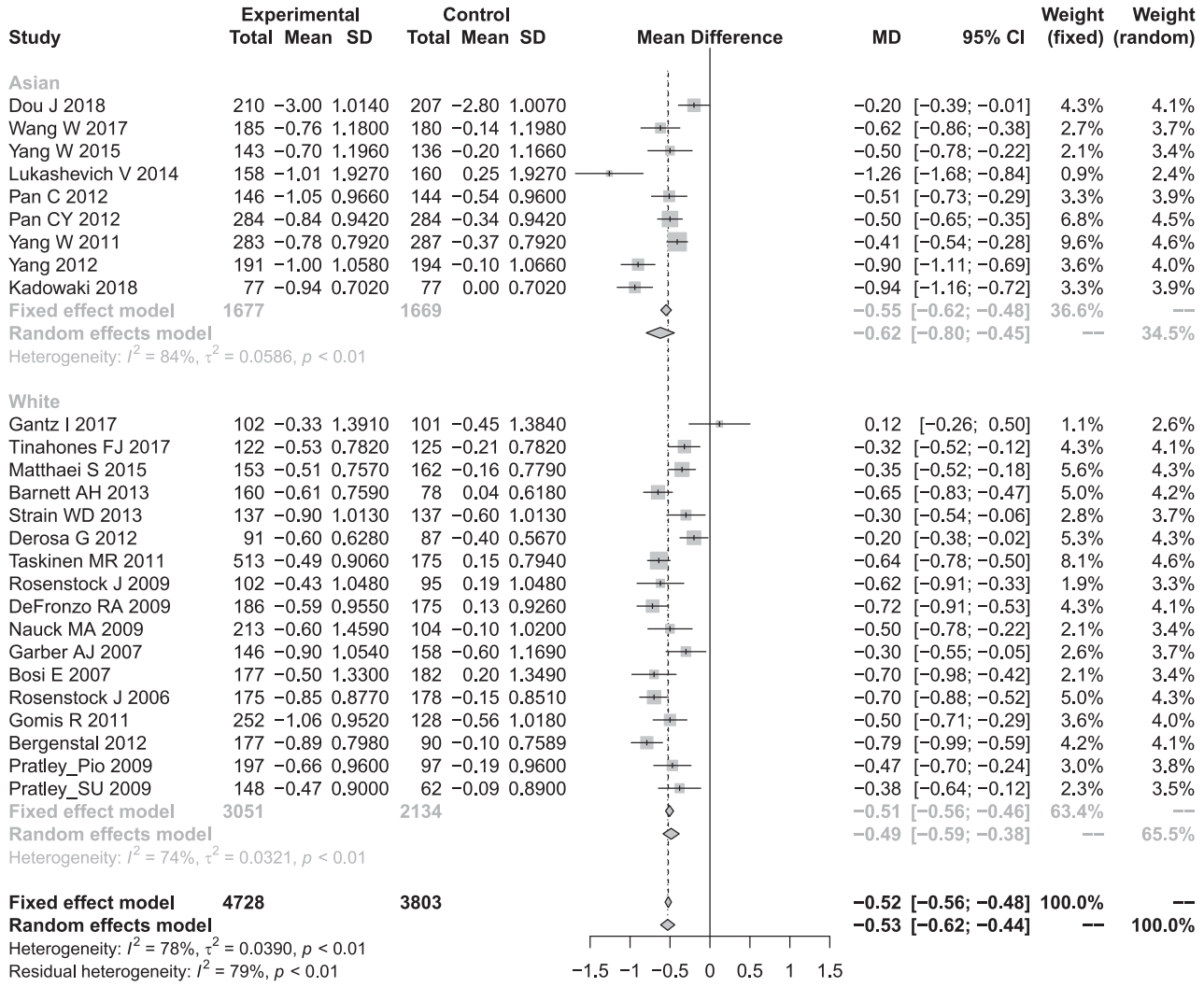

Figure 1—Forest plot for white- and Asian-dominant groups for DPP-4i. See references 24–49 for complete citations.

SGLT-2i

Search Results and Study Characteristics

Sixteen articles were included in the study from the 555 articles that were identified from the database (Supplementary Fig. 2*A*). The total number of study participants was 4,189, of whom 2,178 were randomized in the treatment group and 2,011 were from placebo group. The white-dominant group (nine studies) consisted of 3,015 participants, of whom 1,515 participants were randomized in the treatment group and 1,500 participants in the placebo group. The Asian-dominant group (seven studies) consisted of 1,174 participants, of whom 663 participants were randomized in the treatment group and 511 participants in the placebo group. The summary of included studies is shown in Supplementary Table 1.

Quality of Included Studies and Publication Bias Assessments

All of the studies were double-blind for the participants and personnel. For the adequacy of sequence generation, five studies were categorized as unclear, eight studies were categorized as low risk, and three studies were categorized as high risk. The allocation concealment was unclear in 4 studies, 11 studies were at low risk, and 2 studies were at high risk. There was no particular indication of incomplete data, selective reporting, or other biases in any of the included studies (Supplementary Table 1*B* and Supplementary Fig. 2*B*). The Egger test and funnel plot suggested that there was no asymmetric pattern and no particular concern regarding a publication bias (Supplementary Fig. 2*B* and *C*).

Efficacy Outcomes

HbA_{1c} data were pooled from the 16 comparison pairs from 16 studies. Overall, the difference between the treatment group and comparison group was −0.79 (95% CI −0.91, −0.66; I^2 = 80%) favoring treatment (Fig. 2). In the white-dominant group, the difference between treatment group and comparison group was −0.64 (95% CI −0.74, −0.53; I^2 = 44%) favoring treatment. In the Asian-dominant group, the difference between treatment and comparison groups was −0.96 (95% CI −1.10, −0.82; I^2 = 66%] favoring treatment. Testing for subgroup differences (random effects model) showed a significant difference (P = 0.0003) between the two groups (Supplementary Table 2*A*).

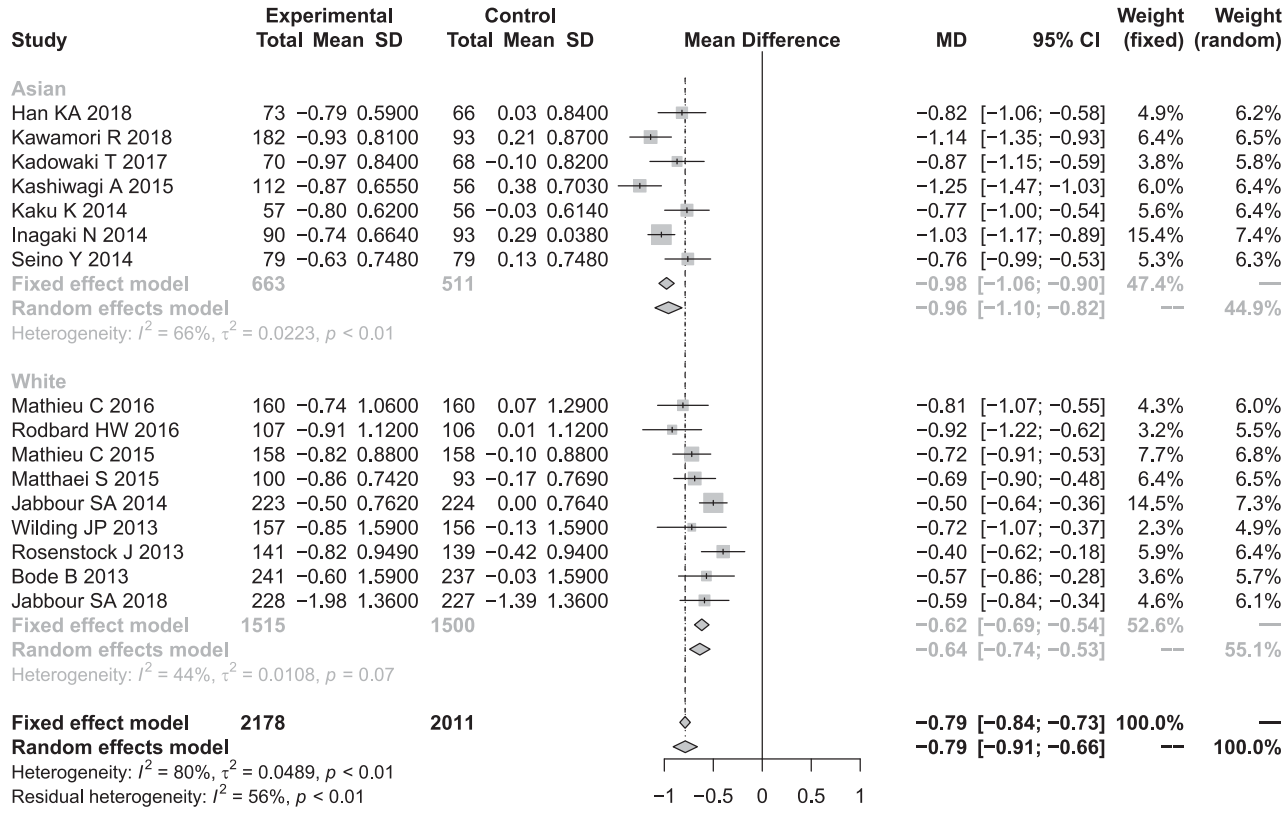

Figure 2—Forest plot for white- and Asian-dominant groups for SGLT-2i. See references 50–65 for complete citations.

Exploratory Analysis

The median duration of diabetes was 8.3 years (range 5.64–12.3) in the white-dominant group and 7.49 years (4.72–11.6) for the Asian-dominant group. The median HbA_{1c} at baseline was 8.17% (7.8–9.3) in the white-dominant group and 8.18% (7.9–8.45) in the Asian-dominant group. The median BMI at baseline was 31.9 kg/m^2 (31.2–33.3) in the white-dominant group and 25.59 kg/m^2 (25.07–26.0) among the Asian-dominant group.

Meta-Regression

The univariate meta-regression analysis showed that percentage of participants who were white ($P < 0.01$) and BMI at baseline ($P = 0.01$) are associated with change in HbA_{1c} from baseline. On the other hand, age ($P = 0.38$), HbA_{1c} at baseline ($P = 0.80$), duration of diabetes ($P = 0.85$), and percentage of participants who were men ($P = 0.1$) were not associated with change in HbA_{1c} from baseline (Supplementary Table 3 and Supplementary Fig. 5).

Sensitivity Analysis

Including five additional studies between 12 and 24 weeks' duration, we pooled HbA_{1c} data from 21 comparison pairs from 21 studies. Overall, the difference between the treatment group and comparison group was −0.70 (95% CI −0.82, −0.58; $I^2 = 84\%$) favoring treatment (Supplementary Fig. 2*E*). In the white-dominant group, the difference between treatment group and comparison group was −0.57 (95% CI −0.69, −0.44; $I^2 = 69\%$) favoring treatment. In the Asian-dominant group, the difference between treatment and comparison groups was −0.85 (95% CI −1.03, −0.66; $I^2 = 87\%$) favoring treatment (Supplementary Fig. 2*E*). Test for subgroup differences (random effects model) showed a difference ($P = 0.0182$) between the two groups (Supplementary Table 2*B*).

GLP-1RA

Search Results and Study Characteristics

A total of 1,481 articles were identified from the database and 4 articles were identified from references of other articles, from which 22 articles were included in the meta-analysis (Supplementary Fig. 3*A*). A total of 23 comparison pairs were retrieved, which satisfied the selection criteria. The total number of study participants was 6,559, of whom 3,608 were randomized in the treatment group and 2,951 were from placebo group. The white-dominant group (19 studies, 20 arms) consisted of 5,682 participants, of whom 3,608 participants were randomized in the treatment group and 2,951 participants in the placebo group. The Asian-dominant group (three studies) consisted of 877 participants, of whom 438 participants were randomized in the treatment group and 439 participants in the placebo group. A summary of included studies is shown in Supplementary Table 1.

Quality of Included Studies and Publication Bias Assessments

All the 22 of the studies achieved the double blindness for the participants and the personnel. For the adequacy of sequence generation, 14 studies were categorized as unclear and 8 studies were categorized as low risk. The allocation concealment was unclear in 6 studies, and 16 studies were at low risk. There was no particular indication of incomplete data, selective reporting, or other biases in any of the included studies (Supplementary Table 1*C* and Supplementary Fig. 3*B*). The Egger test and funnel plot suggested that there was no asymmetric pattern and no

particular concern regarding a publication bias (Supplementary Fig. 3*C* and *D*).

Efficacy Outcomes

HbA_{1c} data were pooled from the 23 comparison pairs from 22 studies. Overall, the difference between the treatment group and comparison group was −0.78 (95% CI −0.88, −0.69; I^2 = 79%) favoring treatment (Fig. 3). In the white-dominant group, the difference between treatment group and comparison groups was −0.79 (95% CI −0.89, −0.69; I^2 = 77%) favoring treatment. In the Asian-dominant group, the difference between treatment and comparison groups was −0.76 (95% CI −1.19, −0.33; I^2 = 90%) favoring treatment (Fig. 3). Test for subgroup differences (random effects model) showed no statistically significant difference (P = 0.8957) between the two groups (Supplementary Table 2*A*).

Exploratory Analysis

The median duration of diabetes was 7.6 years (range 2.8–13.6) in the white-dominant group and 9.3 years (4.0–13.7) for the Asian-dominant group. The median HbA_{1c} at baseline was 8.1% (7.5–9.3) in the white-dominant group and 8.54% (7.95–8.6) in the Asian-dominant group. The median BMI at baseline was 32.94 kg/m^2 (29.9–36.9) in the white-dominant group and 25.4 kg/m^2 (25.3–26.8) in the Asian-dominant group.

Meta-Regression

The univariate meta-regression analysis showed age (P = 0.98), percentage of participants who were white (P = 0.99), HbA_{1c} at baseline (P = 0.99), duration of diabetes (P = 0.54), percentage of participants who were men (P = 0.59), and BMI at baseline (P = 0.94) were not significantly associated with change in HbA_{1c} from baseline (Supplementary Table 3 and Supplementary Fig. 6).

Sensitivity Analysis

Including four additional studies that were identified between 12 and 24 weeks' duration, we pooled HbA_{1c} data from 27 comparison pairs from 26 studies. Overall, the difference between the treatment group and comparison group was −0.79 (95% CI −0.88, −0.70; I^2 = 76%) favoring treatment (Supplementary Fig. 3*E*). In the white-dominant group, the difference between treatment group and comparison group was −0.79 (95% CI −0.89, −0.70; I^2 = 75.1%) favoring treatment. In the Asian-dominant group, the difference between treatment and comparison groups was −0.79 (95% CI −1.03, −0.54; I^2 = 82%) favoring treatment (Supplementary Fig. 3*E*). Testing for subgroup differences (random effects model) showed no statistically significant difference (P = 0.9657) between the two groups (Supplementary Table 2*B*).

DISCUSSION

The current systematic review and meta-analysis focuses on the HbA_{1c}-lowering efficacy of DPP-4i, SGLT-2i, and GLP-1RA in ethnically white and

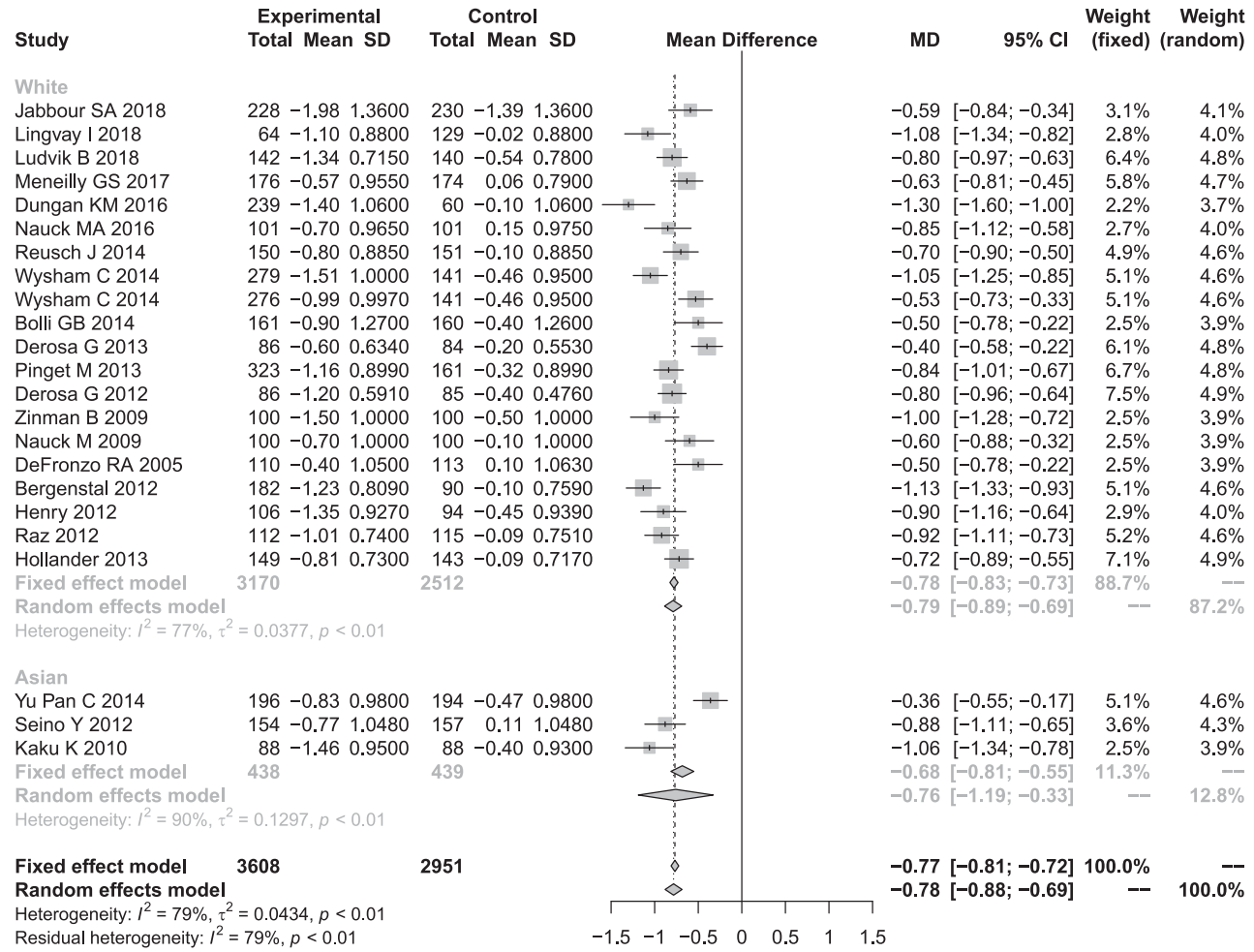

Figure 3—Forest plot for white- and Asian-dominant groups for GLP-1RA. See references 47, 65–85 for complete citations.

Asian participants. Compared with whites, Asians respond better to SGLT-2i. Even though the primary analysis of DPP-4i showed no difference in response to DPP-4i between the two groups, the sensitivity analysis including shorter duration studies did show that Asians respond better to DPP-4i than whites, in keeping with previous reports. No difference was found in the response to GLP-1RA between Asians and whites.

This is the first meta-analysis that reports glycemic response to SGLT-2i by ethnicity. Our results showed that the Asians respond better to SGLT-2i compared with the white-dominant group. In the meta-regression, the percentage of the population who were white and BMI at baseline were associated with HbA_{1c} reduction, whereas baseline HbA_{1c} was not correlated. A recent meta-analysis showed that efficacy and safety of SGLT-2i were favorable in East Asian patients with type 2 diabetes (13). It is interesting to know that SGLT-2i also show greater, albeit nonsignificant, cardiovascular risk reduction in Asians compared with other ethnic groups (18).

Although no significant difference was found between the two groups for DPP-4i, the reduction in HbA_{1c} levels at study end point was greater for the Asian-dominant studies (between-group difference $P = 0.1919$). However, our sensitivity analysis that included studies of shorter duration (from 12 weeks) did show a −0.11% significantly greater reduction in HbA_{1c} in the predominantly Asian group compared with the predominantly white population. A previous meta-analysis by Kim et al. (9) reported that DPP-4i showed greater HbA_{1c}-lowering effect in Asian-dominant studies than in non–Asian-dominant studies (between-group difference −0.18%, $P = 0.006$). In another review, Ito et al. (19) hypothesized that DPP-4i had greater efficacy among East Asian participants than their white counterparts due to the different pathophysiology of type 2 diabetes between the two ethnic groups. Interestingly, these two meta-analyses also included studies of 12 weeks' duration or longer. Finally, in an individual-level analysis of Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS), Davis et al. (20) showed that the greatest initial reduction of HbA_{1c} was observed in East Asians on sitagliptin. It is not clear why our primary analysis based upon studies of at least 24 weeks showed a smaller difference between ethnic groups; there was no obvious difference or bias introduced in the shorter-duration studies, but the results would suggest that the difference seen at 12 weeks does not persist to 24 weeks or longer. Previous studies on sitagliptin and vildagliptin have reported that the clinical pharmacokinetic characteristics of DPP-4i were not different among Asians, blacks, Hispanics, and whites, suggesting that differences in response are more likely to reflect phenotypic or pathophysiological differences (21,22). Lower BMI has been reported to be associated with a better glycemic response (23), yet in the current study, the meta-regression showed no correlation between age, BMI at baseline, percentage of participants who were white, HbA_{1c} at baseline, duration of diabetes, percentage of participants who were men, and HbA_{1c} reduction. This meta-regression suggests that the greater HbA_{1c} reduction seen in Asians in our meta-analysis is not driven by the higher HbA_{1c} at recruitment in the Asian populations. There may, however, be other differences between ethnic groups that are not captured in the recorded baseline characteristics, such as adherence, that could have contributed to differences in results. The use of other glucose-lowering agents in the trials was quite similar between Asian- and white-dominant studies and, hence, is unlikely to explain ethnic differences in treatment efficacy (Supplementary Table 4).

In the present meta-analysis, no difference in efficacy was found between the white- and Asian-dominant groups ($P = 0.8957$) among the studies of GLP-1RA. In a previous meta-analysis conducted on glucagon-like peptide 1 analogs by Kim et al. (10), it was found that HbA_{1c} reduction from baseline was greater in Asian-dominant groups than in non–Asian-dominant groups. The fact that we show no evidence of difference in response between Asians and whites is at odds with this previous report. However, unlike for DPP-4i, for GLP-1RA, inclusion of shorter-duration studies in our analysis, similar to that of Kim et al., did not make any difference to the estimate of efficacy difference. Even though our study had only three Asian studies included, these differed from that of the three Asian studies included by Kim et al. in their meta-analysis. Thus, our lack of replication of the previous meta-analysis may reflect this small number of studies and heterogeneity between studies in the Asian population.

The only remaining differences were that in our study design, to ensure separation between studies reporting efficacy in whites versus Asians, we defined a population cutoff of 70%, whereas Kim et al. used a 50% cutoff, and we only included studies that had 50 patients per treatment arm.

There are some limitations to this study. First, this systematic review and meta-analysis is based on summarized data of RCT studies. Further investigation of individual-level trial data based on ethnicity is required to confirm the reported differences for SGLT-2i and DPP-4i. Second, due to lack of enough studies that satisfied our inclusion and exclusion criteria, studies could not be separated based on South Asians and East Asians. It is known from previous reports that South Asians and East Asians are ethnically heterogeneous, and this demands that more studies be conducted in the South Asian region (14).

In conclusion, the glucose-lowering efficacy of SGLT-2i and DPP-4i was higher in the Asian-dominant group compared with the white-dominant group but not for and GLP-1 analogs. Our data suggest that, if our results are replicated by individual-level patient analyses from clinical trials, ethnicity should be incorporated into the treatment guidelines.

Further studies would also be warranted as to the physiological or pharmacological basis of these differences, given the reported β-cell deficiency and visceral adiposity in Asians.

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Duality of Interest. E.R.P. has received honoraria for speaking from Eli Lilly. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. S.G. researched data and wrote the manuscript. A.Y.D. researched data and reviewed and edited the manuscript. L.A.D. contributed to the discussion and reviewed and edited the manuscript. A.T.N.N. researched data and reviewed the manuscript.

C.N.A.P. reviewed the manuscript. V.M. reviewed and edited the manuscript. E.R.P. researched data and reviewed and edited the manuscript. E.R.P. 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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