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ARTICLE

Comparison of Efficacy of Dipeptidyl Peptidase-4 Inhibitors and Sodium-Glucose Co-Transporter 2 Inhibitors Between Japanese and Non-Japanese Patients: A Meta-Analysis

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We explored efficacy of dipeptidyl peptidase-4 inhibitors (DPP-4is) and sodium-glucose co-transporter 2 inhibitors (SGLT2is) between Japanese and non-Japanese patients with type 2 diabetes mellitus by conducting a systematic review and meta-analysis. A literature search of public databases before May 2017 identified 91 (DPP-4i) and 63 (SGLT2i) randomized placebo-controlled trials (> 12-week treatment). Multivariate meta-regression analysis identified baseline hemoglobin A1c (HbA1c) levels and placebo responses as covariates affecting efficacy of two agent classes independently of study region (Japanese/non-Japanese). When accounted for covariates, DPP-4i caused more pronounced HbA1c reduction in Japanese studies than in non-Japanese studies by 0.18% difference ($P < 0.05$) while causing no difference in fasting plasma glucose reduction between regions. On the other hand, when adjusted by baseline HbA1c levels and placebo responses, efficacy of SGLT2i were comparable between regions. The contrasting results for two agent classes indicate that drug efficacy is affected by different pathophysiology at its therapeutic action point.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Few multiregional clinical trials (MRCTs) have been conducted including Japan in development of drugs for type 2 diabetes mellitus (T2DM). Mechanism underlying ethnic differences in efficacy of dipeptidyl peptidase-4 inhibitors (DPP-4is) is still unclear.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Do DPP-4is and sodium-glucose co-transporter 2 inhibitors (SGLT2is) show ethnic differences in their efficacy, and which factors are predictors of such differences?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ DPP-4i, which enhances postprandial insulin secretion, lower HbA1c levels to a greater extent in Japanese than in non-Japanese patients with T2DM, whereas the reduction in fasting plasma glucose levels is comparable. Homeostasis model assessment of beta-cell function may be a good predictor for the efficacy of DPP-4i. SGLT2i efficacy, which is independent of insulin secretion, is similar between countries.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Our findings will add knowledge to how ethnic differences in efficacy of diabetic agents can be expected, which may increase the feasibility to conduct MRCTs in T2DM areas.

Multiregional clinical trials (MRCTs) may increase the efficiency of drug development and provide faster access to new drugs for patients worldwide. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has recently issued "General principles for planning and design of Multi-Regional Clinical Trials" as an ICH E17 guideline in 2017[1]; the guideline directs the proper design and execution of MRCTs and suggests the consideration of potential intrinsic and/or extrinsic factors differentially affecting subjects' responses to drugs across regions. However, this guidance does not recommend that conducting MRCTs be avoided when intrinsic and/or extrinsic ethnic differences are expected but proposes that information about potential ethnic differences be collected at an earlier stage of the clinical development and considered when designing MRCT protocols.

In type 2 diabetes mellitus (T2DM), few MRCTs for new drug applications have been conducted in Japan, probably to avoid the unclear effect of ethnic factors, such as differences in the pathophysiology of diabetes or in dietary habits, on efficacy, and safety. T2DM in Japanese patients

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predominantly exhibits decreased insulin secretion with low body mass index (BMI), in contrast to that in white patients who are characterized by increased insulin resistance with high BMI.[2,3] Although clinical trials conducted solely in one country would have the advantage of providing robust data on the specific population, it is important to understand the ethnic differences in antihyperglycemic agents (AHAs) to accelerate the global simultaneous development of future diabetes medications and/or to share clinical data globally. Dipeptidyl peptitase-4 inhibitors (DPP-4is) are one of the most widely used classes of oral AHAs, available worldwide since 2006. DPP-4is exert their action via the inhibition of an enzyme, dipeptidyl peptidase-4, increasing concentrations of endogenous incretins (glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide), which are hormones secreted in response to food intake, and result in the enhancement of insulin secretion. Several meta-analyses have reported that DPP-4is cause greater hemoglobin A1c (HbA1c) reduction in Japanese than in non-Japanese patients, or in Asians than in non-Asians patients.[4–9] Our previous systematic review of DPP-4i was unique in focusing on the relationship between DPP-4 inhibition rate and their glucose-lowering efficacy; it demonstrated that DPP-4i cause significantly greater reduction of HbA1c, but not of fasting plasma glucose (FPG), in Japanese than in non-Japanese studies, despite comparable DPP-4 inhibition rates.[10] This study clearly indicated that ethnic differences in the response to DPP-4i exist in the pathway after DPP-4 inhibition and FPG reduction. However, the evidence of ethnic differences in DPP-4i-induced FPG reduction is controversial. For instance, Cai *et al*.[7,9] reported no differences in DPP-4i FPG lowering effect between geographic regions, whereas Kim *et al*.[5] and Berhan *et al*.[6] reported greater FPG reduction in Asians than in non-Asians, or in Japanese than in non-Japanese patients. These reports indicate that it is still unclear whether DPP-4i mechanism of action through enhancement of insulin secretion is related to the mechanism of ethnic differences in their effects on HbA1c and/or FPG. In addition, although past meta-analyses have discussed the possibility that different insulin secretion ability might explain the regional difference, they could not provide clear evidence. Therefore, approach of assessing the efficacy profile (of more than one glycemic parameter) of DPP-4i with another AHA with distinct mechanism of action may be meaningful.

In this study, we performed a systematic review and a meta-analysis of two classes of oral antidiabetic medications, DPP-4i and the newest class of oral AHAs, acting independently of insulin secretion, sodium-glucose co-transporter 2 inhibitors (SGLT2is), to examine whether SGLT2is show similar ethnic differences in efficacy as DPP-4is.

METHODS

Study selection

A systematic review was conducted based on a predefined review protocol. The literature search was conducted from February to May 2017 in PubMed (MEDLINE), EMBASE, and the Japan Medical Abstracts Society. Search terms were determined based on the Patient, Intervention, Control, and Outcome model, except for "Outcome": "Type 2 diabetes mellitus" for "Patient," "DPP-4i" or "SGLT2i" for "Intervention," and "placebo" for "Control." Study type was restricted to "randomized controlled trial." After reviewing the papers based on their titles and abstracts, full-text papers were retrieved and reviewed. In addition, Japanese new drug applications (especially module 2.7.6: summary of clinical studies), and review reports written in Japanese, available from the Pharmaceuticals and Medical Devices Agency (PMDA) homepage (https://www.pmda.go.jp/) by January 2017, were reviewed. The review was performed independently by Y.I. and T.H./M.K., and any discrepancies between the authors were discussed until an agreement was reached. The systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines.[11]

Inclusion criteria for applicable studies were as follows: (i) studies including patients with T2DM (≥ 18 years old), (ii) treatment with DPP-4 or SGLT2i once daily for a minimum of 12 weeks, (iii) treatment as monotherapy or add-on to other AHAs (add-on therapy), (iv) double-blind randomized placebo-controlled design, and (v) available data on HbA1c and FPG change from baseline after treatment. *Post hoc* analyses, studies in elderly patients, patients with renal or hepatic impairment, impaired glucose tolerance, or kidney implantation were excluded. Treatment duration of at least 12 weeks was collected, because HbA1c reflects daily glucose level of the past 1 to 2 months. Only once-a-day dosing was collected to avoid blood glucose concentration variance due to different dosing frequencies among studies.

Data extraction

From studies meeting the above criteria, data regarding baseline characteristics (such as mean age, percentage of male patients, percentage of Asian patients, and mean BMI) and efficacy variables (change from baseline HbA1c and FPG values vs. placebo and their SE or confidence interval (CI)) were extracted to a prespecified datasheet independently by Y.I. and T.H./M.K., and any discrepancies between the authors were resolved by discussion and/or reconfirmation of the data in the original paper. The ClinicalTrials.gov (https://clinicaltrials.gov/) database was also searched to supplement missing data.

Authors determined the category of study region based on information of study participating countries. Studies were classified as "Japanese" when conducted locally in Japan, and "non-Japanese" when conducted outside of Japan, including MRCTs. If Japan was one of the participating countries in MRCTs, studies were classified as "non-Japanese" for the analysis. The percentage of Asian subjects in Japanese studies was assumed to be 100%.

For Japanese studies, in which baseline HbA1c levels were reported in the Japan Diabetes Society (JDS) values, conversion into National Glycohemoglobin Standardization Program (NGSP) values was performed using the following formula: HbA1c (NGSP) (%) = 1.02 × HbA1c (JDS) (%) + 0.25%.[12] For the change from baseline or change vs. placebo, no conversion was utilized, because minor differences in JDS or NGSP values were expected. FPG values reported in mmol/L were converted to mg/dL by the following formula: FPG (mg/dL) = FPG (mmol/L) × 18. Missing data were calculated by other information whenever possible. For example, if the baseline

characteristics were not reported for the total population but reported for each arm, the mean values of the study were calculated from each arm. When either homeostasis model assessment of beta-cell function (HOMA-β), homeostasis model assessment of insulin resistance (HOMA-IR), or serum insulin (μU/mL) values were not available, a calculation was adopted using the FPG (mg/dL) value.

- HOMA-IR = FPG × insulin/405
- HOMA-β = insulin × 360/(FPG – 63)
- Insulin = (405 × HOMA-IR)/FPG

Data from the treatment groups with "clinical dose" were used for the analyses; we defined "clinical dose" as a dose approved in the Unites States, Europe, or Japan as the usual dose regimen (including uptitration). However, for gemigliptin and evogliptin, which were approved only in Korea, treatment groups of the "approved in Korea" doses were included in the analyses. If more than one clinical dose group was available in a study (e.g., dose-response study), we selected the maximum dose group for analyses. If there was more than one maximum clinical dose group with different times of drug administration, data from the morning dose group were adopted.

Mean differences of HbA1c and FPG (change from baseline vs. placebo) and their SEs were used for the meta-analysis. If the SE of mean difference was not available from papers, SE was calculated from CI whenever possible.

Assessment of risk of bias

Risk for individual studies was assessed using the Cochrane's tool risk of bias.[13] Two authors (Y.I. and T.H.) independently reviewed full-text papers and determined the risk level (low, unclear, or high) for the following seven factors: (i) random sequence generation (selection bias), (ii) allocation concealment (selection bias), (iii) blinding of participants and personnel (performance bias), (iv) blinding of outcome assessment (detection bias), (v) incomplete outcome data (attrition bias), (vi) selective reporting (reporting bias), and (vii) other bias.

The risk of bias due to "incomplete outcome data" was assessed as other than low when the total discontinuation rate was ≥ 20% and/or the discontinuation rate was imbalanced being at least twice more frequent in one treatment group than in the other. Any discrepancy in the assessment between the authors was discussed until an agreement was reached. Publication bias was assessed graphically by forest plot and statistically by Egger's test.

Statistical analysis

Meta-analyses were performed using the random effects model, which allows that the true effect size may vary from study to study.[14] I^2 was used to determine the heterogeneity of the pooled studies. I^2 (range of 0–100%) reflects what proportion of the observed variation is real, and can be calculated by formula I^2 = (Q-df)/Q × 100% (Q: Cochran's Q, df: degree of freedom).[15] When heterogeneity was considered large ($I^2 \geq 50\%$) in the initial analysis, factors that correlate with the effect size were explored by univariate meta-regression analysis. The impact of the study region, when adjusted for those factors, was statistically examined by execution of multivariate meta-regression analysis. To confirm the robustness of the result, sensitivity analyses was performed for the following: (i) excluding from the "non-Japanese study" category MRCTs with Japanese participants, (ii) monotherapy studies only, and (iii) excluding studies with high risk of bias. In addition, secondary analyses were performed in subset of studies according to factors that correlated with efficacy. In all analyses, the level of statistical significance was defined as $P < 0.05$. Meta-analysis was performed using Review Manager (version 5.3; Nordic Cochrane Centre, Copenhagen, Denmark). Egger's test and meta-regression analysis were performed using JASP (version 0.9; JASP Team (2018)).

RESULTS

Systematic review and characteristics of included studies

The literature search of medical databases identified 829 (DPP-4i: 397 and SGLT2i: 432) potential papers, for which the abstracts and titles were reviewed by two independent reviewers (**Figure 1**). After excluding ineligible papers, full-text of 280 papers were reviewed, of which 144 studies were deemed applicable for analysis. We identified additional 571 (DPP-4i: 349 and SGLT2i: 222) potential studies from Japanese new drug applications and their review reports by PMDA through search of the PMDA website (http://www.pmda.go.jp/index.html), from which 99 studies were deemed applicable for analysis. After data extraction, integration of applicable studies, and supplementation of the missing data from the ClinicalTrials.gov website (https://clinicaltrials.gov/), we excluded 89 studies because of duplication, lack of SE or CI reported for HbA1c and/or FPG outcomes, or patients not being treated with a clinical dose (see the Method section for definition of "clinical dose"). Finally, data of 154 (DPP-4i: 93 and SGLT2i: 61) studies were applied to the meta-analysis. Study information is shown in **Table S1**. Sixty-nine of 93 DPP-4i studies and 42 of 61 SGLT2i studies were non-Japanese studies (**Figure 2**). In non-Japanese studies, 35% and 37% of patients were Asian in DPP-4i and SGLT2i studies, respectively. Two studies, Roden *et al.*[16] and Lewin *et al.*[17], were MRCTs, in which ~ 20% of participants were from Japan. Add-on therapy studies were the dominant (78.6%) of SGLT2i non-Japanese study (**Figure 2**). Characteristics of included studies reflected typical patients with T2DM; mean BMI and HOMA-β and HOMA-IR were lower in Japanese studies than in non-Japanese studies (**Figure 3**).

The risk of bias for each study was assessed in seven domains, as low, high, or unclear in accordance with Cochrane's tool of risk of bias and was presented in a graph (**Figure S1**) and in a summary table (**Figure S2**). Overall quality of the individual studies included in the meta-analysis was considered acceptable. Most of the domains for each study were determined as low risk of bias, except for selection bias domains, in which over half of the studies were assessed as unclear risk due to the lack of relevant information; and in the incomplete outcome data domain where 5 of 93 (5.4%) DPP-4i studies and 3 of 61 (4.9%) SGLT2i studies were assessed as high

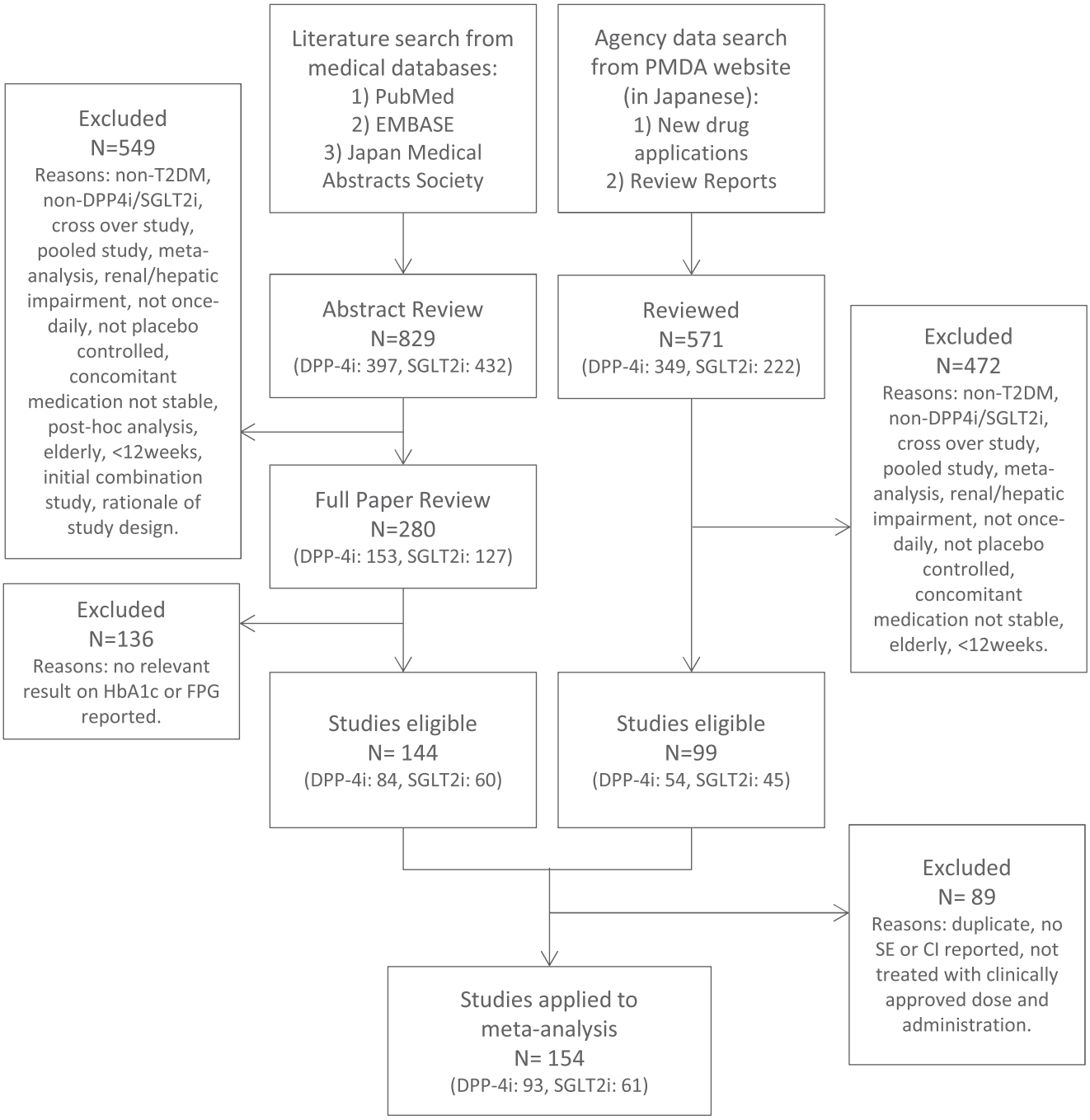

Figure 1 Flowchart of the studies selection. Two independent reviewers searched and reviewed papers and extracted data. Any discrepancies between the authors were discussed until an agreement was reached. ClinicalTrials.gov was searched to supplement missing data. CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; PMDA, Pharmaceuticals and Medical Devices Agency; SGLT2i: sodium-glucose co-transporter 2 inhibitors; T2DM, type 2 diabetes mellitus.

risk of bias. No publication bias was identified from the funnel plot or the Egger's test in DPP-4i studies. In SGLT2i studies, Egger's test identified significant asymmetry for overall population (P = 0.023), which was lost when tested separately in the non-Japanese or Japanese subgroup (**Figure S3**). Overall, publication bias was considered low for studies included in the meta-analysis.

Initial meta-analysis without consideration of covariates: HbA1c and FPG changes from baseline vs. placebo

Initial meta-analysis was performed without consideration of covariates. In the DPP-4i studies, HbA1c reduction (weighed mean difference (95% CI)) was −0.62% (−0.66, −0.59) in non-Japanese and −0.86%

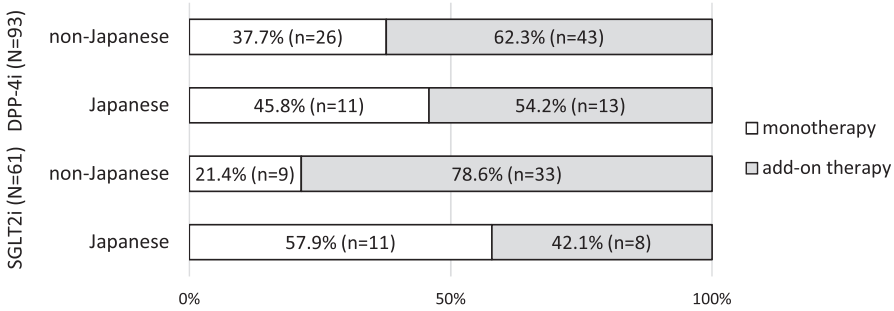

Figure 2 Number of studies applied to meta-analysis by study region and type of therapy. Number of studies applied to meta-analysis by study region (non-Japanese or Japanese) and type of therapy (monotherapy or add-on therapy) is displayed in bar graphs. DPP-4i, dipeptidyl peptidase-4 inhibitors; SGLT2i: sodium-glucose co-transporter 2 inhibitors.

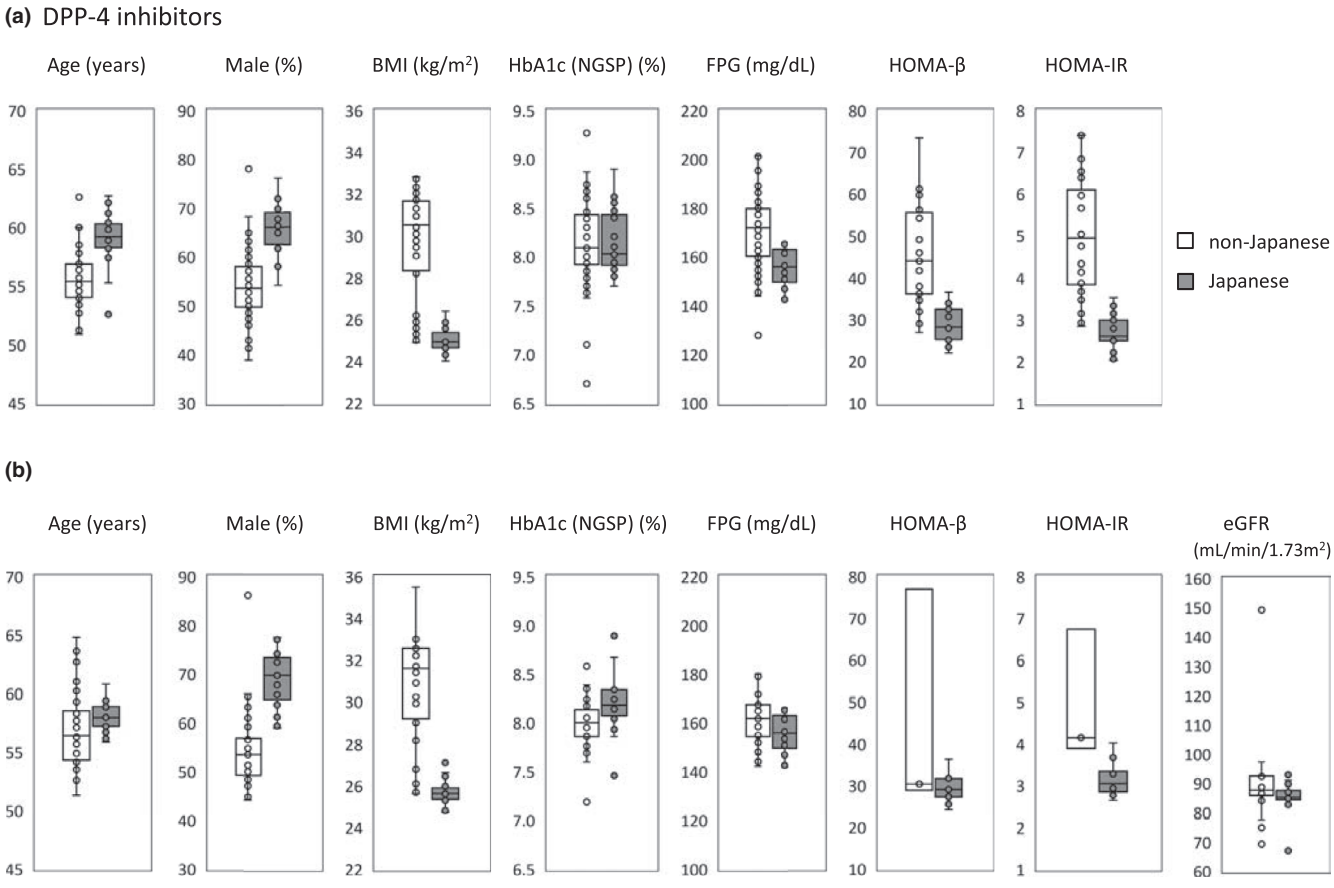

Figure 3 Distribution of baseline characteristics of included studies. Baseline characteristics of included studies are displayed in box plots by (**a**) DPP-4i and (**b**) SGLT2i studies. The length of the box represents the interquarter range (25% quartile to 75% quartile) and the middle line in the box represents the median. White circles and boxes represent non-Japanese studies and black circles and boxes represent Japanese studies. Whiskers are drawn to the maximum or minimum data (up to 1.5 times the length of the interquarter range). Study data beyond whiskers are displayed as outliers. BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HOMA-β, homeostasis model assessment of beta-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; NGSP, National Glycohemoglobin Standardization Program.

(−0.92, −0.81) in Japanese study subgroups, with statistically significant difference between the subgroups. No significant between-subgroup difference was observed in FPG reduction (P = 0.10). The heterogeneity of studies included in each subgroup was moderate (I^2: 49-58%; **Figure 4a**). In the SGLT2i studies, HbA1c reduction was −0.65% (−0.71, −0.60) in non-Japanese and −0.93% (−1.04, −0.82) in Japanese study subgroups, with statistically significant difference between the subgroups. FPG reduction was also significantly larger in Japanese than in non-Japanese studies. However, the heterogeneity of the studies included in each subgroup was substantial

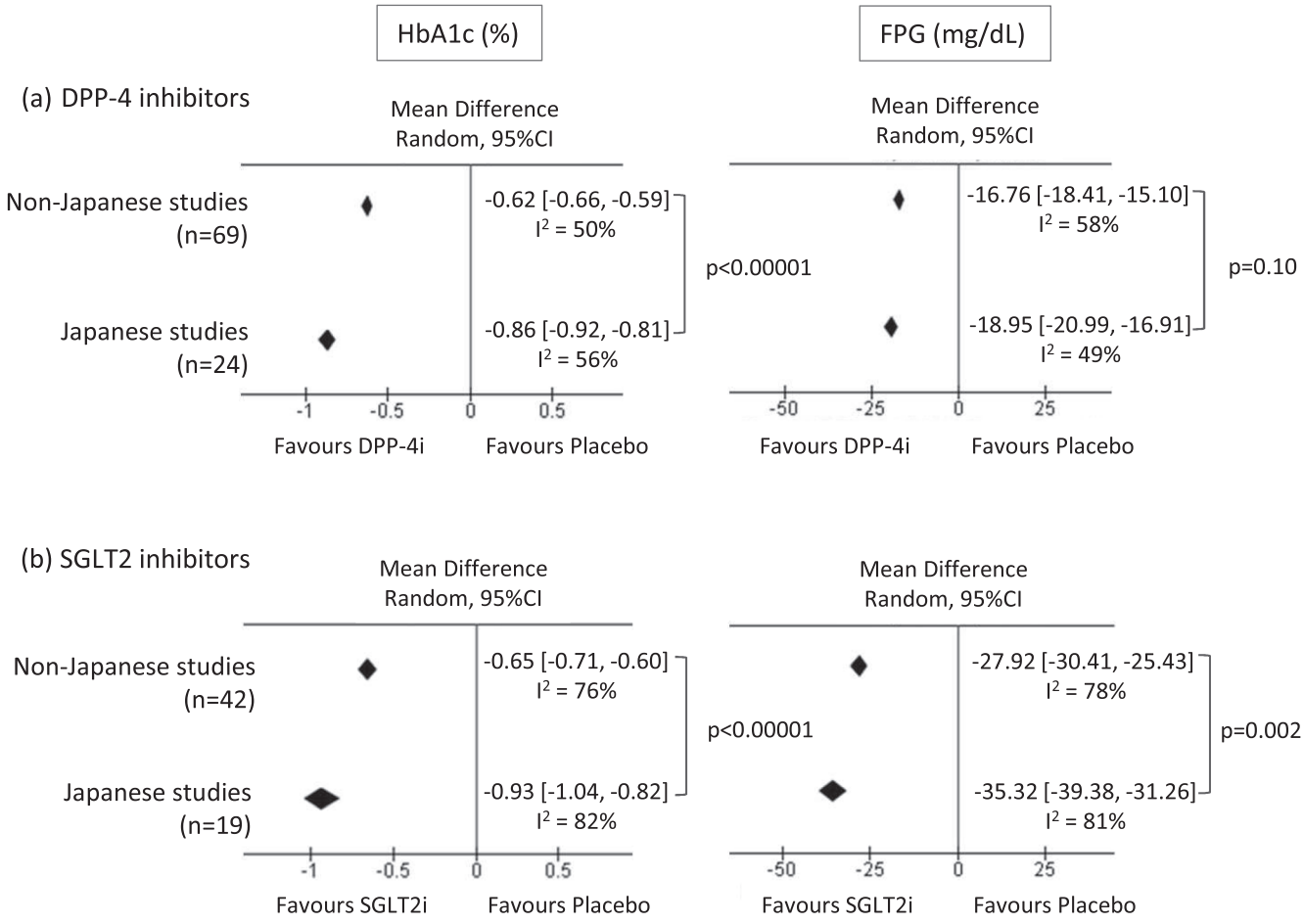

Figure 4 Initial meta-analysis without consideration of covariates: Pooled HbA1c and FPG reduction in (**a**) DPP-4i and (**b**) SGLT2i studies by study region (non-Japanese studies/Japanese studies). Changes from baseline vs. placebo in HbA1c and FPG were pooled by meta-analysis using a random effects model. The diamond center represents weighed mean average and the diamond width represents its pooled 95% CI. CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; SGLT2i, sodium-glucose co-transporter 2 inhibitors;.

(I^2: 76–82%; **Figure 4b**). Data for the individual studies are presented in forest plots in **Figure S4**.

In the sensitivity analyses, HbA1c reduction by DPP-4i was consistently significantly larger in Japanese studies than in non-Japanese studies, despite a comparable FPG reduction, which supported the robustness of the results (**Figure S5**). However, the results of the SGLT2i studies changed drastically when they were limited to monotherapy; both HbA1c and FPG reductions were not different across study regions (*P* value of between-group differences: HbA1c $P = 0.66$, FPG $P = 0.51$). These results suggested that DPP-4i causes a more pronounced HbA1c decrease in Japanese patients than in non-Japanese patients, whereas SGLT2i did not show evidence for a differential ethnic response.

Meta-regression analysis – identification of highly correlated factors with HbA1c reduction

Next, we performed a univariate meta-regression analysis to explore factors that highly correlate with HbA1c reduction by DPP-4i and/or SGLT2i. As a result, several factors with statistical significance were observed in the DPP-4i studies: percentage of male patients, percentage of Asian patients, mean BMI, mean HOMA-β, mean HOMA-IR, and HbA1c change from baseline in the placebo arm. Therapy (monotherapy or add-on therapy), percentage of male patients, percentage of Asian patients, mean BMI, baseline HbA1c, and HbA1c change from baseline in the placebo arm were identified as factors with statistical significance in the SGLT2i studies (**Table S2**). Then, a multivariate meta-regression analysis was applied for each AHA class to identify factors correlating with HbA1c reduction when accounting for study region (non-Japanese/Japanese). Three factors showed statistical significance in either AHA class: (i) HOMA-β (DPP-4i only), (ii) baseline HbA1c (SGLT2i only), and (iii) HbA1c change from baseline in the placebo arm (placebo response; both classes; **Table S3**). Then, we performed a multivariate meta-regression analysis to assess the effect of the study region (non-Japanese/Japanese) when adjusting for baseline HbA1c and placebo response (**Table 1**). As a result, HbA1c reduction by DPP-4i was significantly more pronounced in Japanese than in non-Japanese patients with 0.18% difference. On the other

Table 1 Result of multivariate meta-regression analysis: Effect of study region or HOMA-β on HbA1c reduction versus placebo when adjusted with baseline HbA1c and placebo response

	DPP-4 inhibitors			SGLT2 inhibitors		
Coefficients	**Estimate**	**SE**	***P* value**	**Estimate**	**SE**	***P* value**
Effect of study region (non-Japanese or Japanese) on HbA1c reduction vs. placebo						
Intercept	−0.0345	0.2914	0.905	2.0177	0.6001	< 0.001
Baseline HbA1c (NGSP)	−0.0956	0.0357	0.007	−0.3450	0.0732	< 0.001
ΔHbA1c in placebo arm (%)	−0.3124	0.0653	< 0.001	−0.5460	0.1087	< 0.001
Study region: non-Japanese	0.1798	0.0319	< 0.001	0.0232	0.0582	0.690
Effect of HOMA-β on HbA1c reduction vs. placebo[a]						
Intercept	−0.8982	0.4157	0.031	5.1954	1.9129	0.007
Baseline HbA1c (NGSP)	−0.0153	0.0502	0.761	−0.7200	0.2327	0.002
ΔHbA1c in placebo arm (%)	−0.2952	0.0668	< 0.001	−0.5475	0.2762	0.047
HOMA-β	0.0074	0.0013	< 0.001	−0.0038	0.0044	0.388

ΔHbA1c, change from baseline in hemoglobin A1c; HbA1c, hemoglobin A1c; DPP-4i, dipeptidyl peptidase-4 inhibitors; HOMA-β, homeostasis model assessment of beta-cell function; NGSP, National Glycohemoglobin Standardization Program; SGLT2i, sodium-glucose co-transporter 2 inhibitors.
[a]The analysis incorporating HOMA-β is exploratory, based on small number of studies which reported HOMA-β (50/93 studies of DPP-4i and 14/61 studies of SGLT2i).

hand, HbA1c reduction by SGLT2i was not significant between study regions ($P = 0.690$). Similar result was indicated from exploratory multivariate meta-regression analysis in which HOMA-β data were incorporated: HOMA-β was a significant covariate for HbA1c reduction of DPP-4i, but not for SGLT2i ($P = 0.388$). We found that placebo arms of many non-Japanese studies showed a notable HbA1c decrease from baseline, whereas in Japanese studies many placebo arms showed HbA1c aggravation (**Figure 5**). In addition, we found that in SGLT2i studies, baseline HbA1c values in non-Japanese studies were distributed in a lower range than in Japanese studies. These results suggested that an imbalanced distribution of baseline HbA1c and a placebo effect may have affected the result. Next, we performed a secondary meta-analysis in selected studies with the following characteristics: (i) baseline HbA1c (NGSP): ≥ 7.8% and < 8.6% and (ii) HbA1c change from baseline in the placebo arm: ≥ 0% and < 0.3%. As a result, in DPP-4i studies, the same conclusion was observed with the initial analyses, and the heterogeneity (I^2) of the subgroups mildly improved from 49–58% to 0–57% (**Figure 6a**). In the SGLT2i studies, the difference observed in HbA1c and FPG in the initial analysis was no longer significant in the secondary analysis (HbA1c: $P = 0.45$, FPG: $P = 0.61$; **Figure 6b**), with mild improvement in heterogeneity (I^2) from 76–82% to 50–77%. Based on these results, it was likely that SGLT2i essentially does not show differences in efficacy between Japanese and non-Japanese, when accounting for baseline HbA1c and excluding studies with unnatural placebo responses.

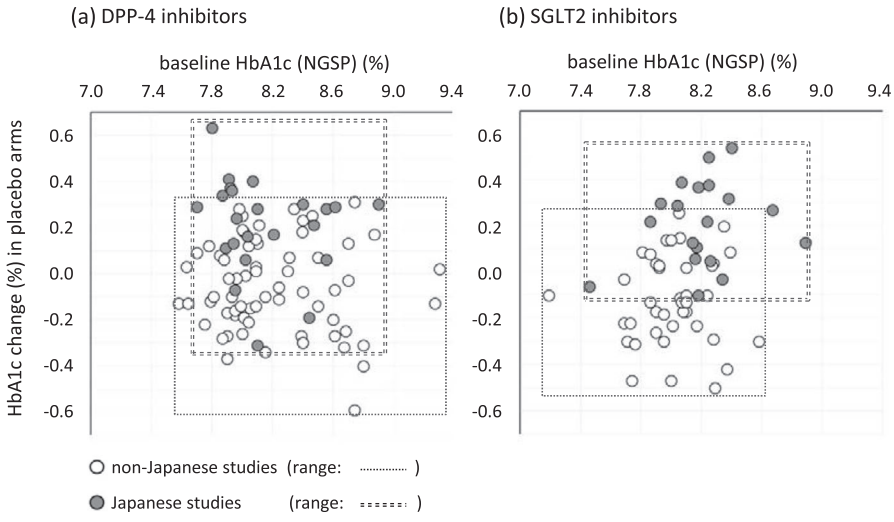

Figure 5 Distribution of "baseline HbA1c" and "placebo response" of studies by study regions (non-Japanese studies/Japanese studies). Each circle represents mean baseline HbA1c (NGSP) (%) and HbA1c change from baseline (%) in the placebo arm of individual (**a**) DPP-4i and (**b**) SGLT2i studies. White circle: non-Japanese studies; black circle: Japanese studies. Single-dotted line represents range of non-Japanese studies, and double-dotted line represents range of Japanese studies. DPP-4i, dipeptidyl peptidase-4 inhibitors; HbA1c, hemoglobin A1c; NGSP, National Glycohemoglobin Standardization Program; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

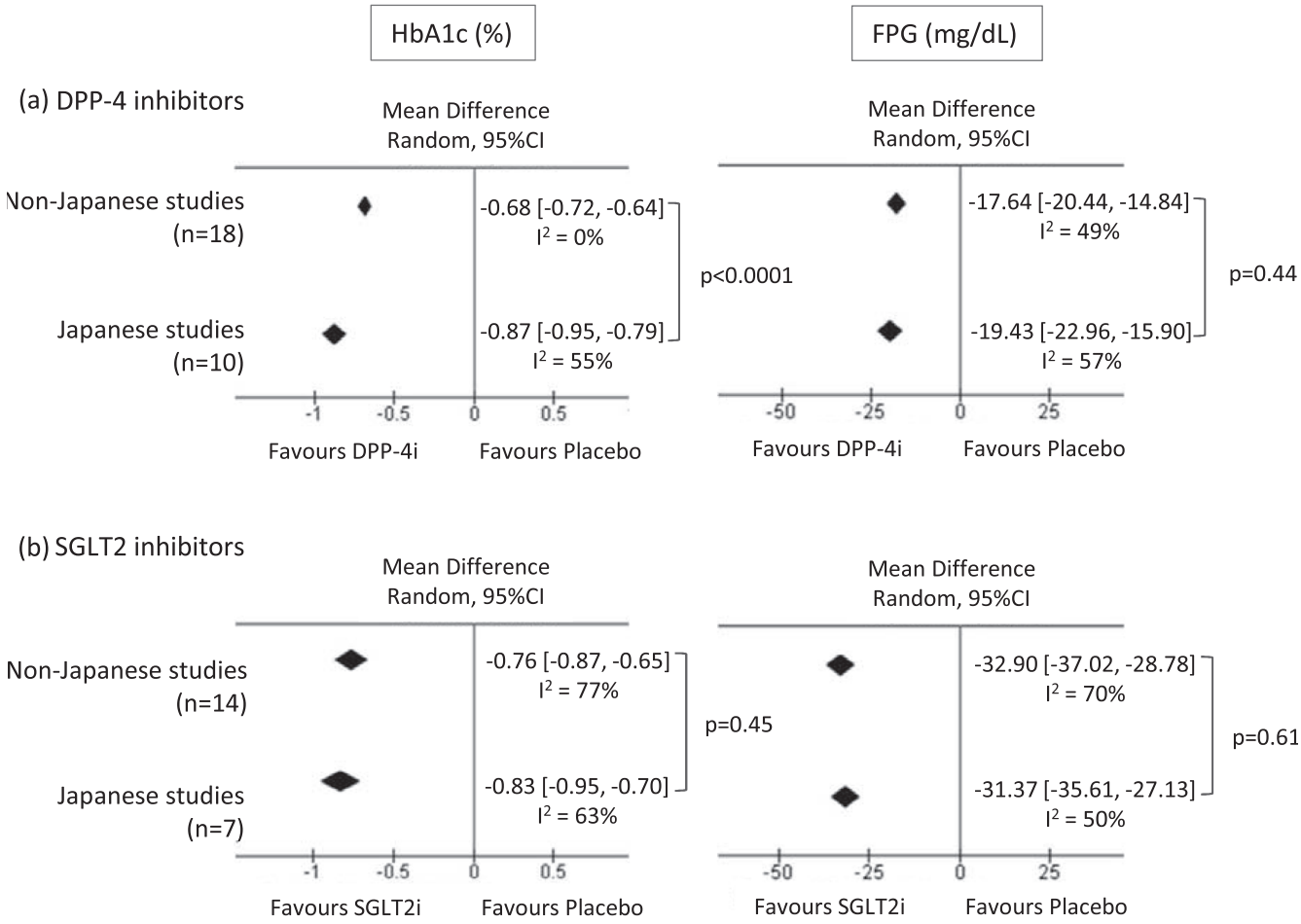

Figure 6 Secondary meta-analysis in consideration of covariates: Pooled HbA1c and FPG reduction of (**a**) DPP-4i and (**b**) SGLT2i studies by study regions, limiting to studies with baseline HbA1c 7.8–8.6% and HbA1c change in the placebo arm 0.0–0.3%. Change from baseline vs. placebo in HbA1c and FPG were pooled by meta-analysis using random effects model in subset of studies. Center of diamond represent weighed mean average and width of diamond represent its pooled 95% CI. CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

DISCUSSION

From our meta-analysis of DPP-4i studies, we clearly demonstrated that DPP-4i cause more pronounced HbA1c reduction in Japanese than in non-Japanese patients, whereas the extent of FPG reduction is comparable. The robustness of this result was supported by several other sensitivity analyses. It was also consistent with our previous systematic review, which has shown ethnic differences between Japanese and non-Japanese studies in relationship between DPP-4 inhibition rate and HbA1c reduction, but not in relationship between DPP-4 inhibition rate and FPG reduction.[10] Our result for FPG is contrary to the results of meta-analyses by Kim *et al*.[5] and Berhan *et al*.,[6] which reported greater FPG reduction in Asian than in non-Asian studies or in Japanese than in non-Japanese studies. Although Kim *et al*.[5] included treatment groups without limitations of the number of doses per day, we limited our protocol to include treatment groups with once-daily administration only, to avoid variance among studies in blood glucose concentration patterns due to different dosing frequency. The meta-analysis by Berhan *et al*.[6] included treatment data for alogliptin (once daily) only, but they did not exclude active-controlled designs. However, the meta-analyses by Cai *et al*.,[7,9] which consisted of mostly once-daily treatment data from a placebo-controlled design, indicated no difference in FPG reduction between Asian and non-Asian studies, which is consistent with our study result. These differences in protocols might have caused the mismatch of FPG results. Considering the mechanism of action of DPP-4i, which is glucose-dependent enhancement of postprandial insulin excretion, DPP-4i may express greater improvement in postprandial glucose levels in Japanese than in non-Japanese patients, which leads to a larger HbA1c reduction (a biomarker reflecting blood glucose concentrations in the past 1 to 2 months), but not in glucose levels during a fasting state. Investigating ethnic differences in postprandial glucose (PPG) reduction caused by DPP-4i may be meaningful, but because few clinical trials assess efficacy of PPG reduction, probably

because the meal tolerance test is time-consuming and burdensome to participating patients, and because the meal content may differ among countries or study sites, the interpretation of meta-analysis results focusing on the PPG-lowering efficacy of DPP-4i seems difficult.[5,9]

SGLT2i is the newest type of oral AHA with unique insulin-independent action. It inhibits SGLT2 in renal proximal tubules, which leads to enhancement of urinary glucose excretion. Although the efficacy of SGLT2i has been tested in and outside of Japan in many clinical trials, only a few meta-analyses have investigated its ethnic difference. Whereas a meta-analysis report described no disparity in the efficacy of SGLT2i between Asians and non-Asians,[18] a review of ipragliflozin pointed out that its efficacy seems to be greater in Japanese studies than in non-Japanese studies, indicating controversial issues about ethnic differences of SGLT2i.[19] Meta-analysis without consideration of covariates showed larger efficacy of SGLT2i in Japanese studies vs. non-Japanese studies, but with substantial heterogeneity in the pooled studies. Sensitivity analysis excluding add-on therapy studies did not show significant difference between regions; which was consistent with the observation that add-on therapy was related to smaller HbA1c reduction by SGLT2i in non-Japanese studies (**Tables S2** and **S3**). The significance between regions was also lost when baseline HbA1c and placebo response were accounted for in the multivariate meta-regression analysis. Our study suggested that an ethnic difference in the glucose-lowering efficacy of SGLT2i between Japanese and non-Japanese studies is unlikely when adjusting for factors affecting efficacy. The above contrasting results for two AHA categories indicate that efficacy of T2DM treatment is affected by differential pathological condition relevant to the point of action of the drug.

The HbA1c reduction by DPP-4i was pronounced by 0.18% in Japanese studies vs. non-Japanese studies after adjusting for baseline HbA1c and placebo effects. The goal of HbA1c levels to reduce the risk of microvascular complication of diabetes is < 7.0%.[20,21] For example, for patients with baseline HbA1c of 8.0%, treatment effect with additional 0.18% reduction would help patients to achieve their treatment goal. We cannot ignore the clinical significance of 0.18% difference when conducting MRCTs, especially for dose-response studies to determine recommended dose by regions.

Our study is unique because we identified HbA1c reduction in the placebo arm as covariate of effect size in both DPP-4i and SGLT2i studies. HbA1c levels in the placebo arms are expected to remain steady or mildly aggravate in general, because participants are essentially in a non-treated state. However, notable decrease of HbA1c in the placebo arms was observed in our non-Japanese studies. Our observation seems consistent with the results of a pooled analysis of patient-level data of vildagliptin, for which placebo responses were reported in white, Chinese, and Indian, but not in Japanese subgroups.[22] Another meta-analysis reported that efficacy of DPP-4i studies conducted in China is lower than that of studies conducted outside of China, due to a notable HbA1c reduction in the placebo arms, whereas a reverse placebo response was observed in Japanese studies.[23] We suggest one of the reasons of high placebo response may be the lack of rigid criteria regarding diet and exercise therapy before the start of study treatment. We noticed that, although most Japanese studies demanded stable diet and exercise therapy for 8 weeks or more before randomization (96% of DPP-4 and 68% of SGLT2i studies), only 26% of DPP-4 and 44% of SGLT2i non-Japanese studies had such criteria. Improvement in diet and exercise therapy after study enrollment would affect HbA1c. Our study is also unique because we attempted to explain the mechanism of difference by baseline "HOMA-β." HOMA-β is an index of beta-cell function, derived from fasting plasma glucose and insulin concentrations,[24] which is known to be lower in Japanese patients with T2DM compared with those of white patients.[2,3] Our exploratory meta-regression analysis incorporating HOMA-β (**Table 1**) supported our conclusion that decreased insulin secretion ability (major reason for most T2DM in Japanese) is related to more pronounced HbA1c reduction of DPP-4i. Several other meta-analyses studies identified correlation between BMI and HbA1c reduction, referring to low BMI as predictor of good response to DPP-4i.[5,9] However, in our multivariate meta-analysis of DPP-4i, BMI was not a significant covariate when study region was accounted for (P = 0.339). Because Japanese patients with T2DM express low insulin secretion at lower BMI than white patients,[3] HOMA-β might be a more appropriate and direct indicator of good DPP-4i response than BMI. Interestingly, the efficacy of SGLT2i did not correlate with HOMA-β (P = 0.846) or with BMI (P = 0.764) in our study. This observation is consistent with a previous report that ipragliflozin efficacy is not affected by BMI or by obesity.[25] Based on these results, we suggest that the glucose-lowering efficacy of DPP-4i is affected by a differential pathological condition (insulin secretion defect or increased insulin resistance), whereas that of SGLT2i, which has an insulin independent mechanism of action, is not.

There are several limitations to our study. First, this study was based on publicly available aggregated data; thus, public bias cannot be completely avoided. Second, although we conducted a systematic review and a meta-analysis with randomized controlled trials to minimize the risk of bias of individual study data, and to rule out arbitrariness in the data-collecting process, subgroups are not randomized and have different background information; therefore, the comparison between subgroups always has an aspect of an observational study. For example, we pooled data of different doses of different compounds in a class. The lower Japanese doses were observed in two drugs, canagliflozin and sitagliptin. However, dose-response studies of canagliflozin[26] and sitagliptin[27] as monotherapy indicated that HbA1c reduction effect reaches "the near maximum effect" in dose ranges between 100 and 300 mg in canagliflozin and 50 and 100 mg in sitagliptin, respectively in Japanese patients. Therefore, we consider the impact of difference in dose distribution between non-Japanese and Japanese studies is little in our study. But still, there may exist a small difference in maximum effect of each compound within the same class, and uneven distribution of compounds may account for some differences between regions. Also, additional analysis (data not shown) indicated that treatment duration affects the

effect size of DPP-4i, which suggests the need to consider for time-course of the effect. Model-based meta-analysis, which is a novel approach to estimate dose-response by incorporating multiple time points and dose information in addition to other covariates,[28,29] may be a useful approach to overcome these limitations. Third, the non-Japanese studies may contain some percentage of Japanese patients who live outside of Japan, or other Asian patients who exhibit the same pattern as Japanese. However, the impact of those potential cases would be small, considering that the two MRCTs with ~ 20% of Japanese patients from Japan did not affect the result (**Figure S5**). Finally, we did not focus on SGLT2i efficacy in weight or blood pressure reduction, and the presence of ethnic differences in these efficacy parameters is unclear.

This is the first meta-analysis that investigated efficacy profile of DPP-4i and SGLT2i in parallel to understand the mechanism why DPP-4i shows ethnic difference. Our study demonstrated an ethnic difference in DPP4i-induced HbA1c reduction, but not in FPG reduction, between Japanese and non-Japanese studies. SGLT2i did not show an ethnic difference in HbA1c and FPG reduction, after accounting for baseline HbA1c and for the response in the placebo arm. The contrasting results for the two AHA categories indicate that differences in the efficacy of T2DM treatment may occur due to different pathophysiology relative to the therapeutic action point of the drug.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Figure S1. Risk of bias graph.
Figure S2. Risk of bias summary.
Figure S3. Funnel plot and Egger's test for asymmetry.
Figure S4. Forest plot of initial meta-analysis presenting outcomes for individual studies
Figure S5. Sensitivity analyses of HbA1c and FPG change from baseline versus placebo.
Table S1. List of included studies.
Table S2. Estimate of each coefficient by univariate meta-regression analysis.
Table S3. Estimate of each coefficient when accounting for study region (non-Japanese/Japanese).

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Conflict of Interest. Y.I. was an employee of MSD K.K., Tokyo, Japan, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA at the time this study was conducted. All other authors declared no competing interests for this work.

Author Contributions. Y.I., K.A., T.H., and M.T. wrote the manuscript. Y.I. and M.T. designed the research. Y.I., T.H., M.K., and K.A. performed the research. Y.I. analyzed the data.

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