Factors related to glucose-lowering efficacy of oral antidiabetics: a systematic review and meta-analysis focusing on ethnicity and study regions

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Abstract

Type 2 diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from lack of insulin action. The mechanism for a lack of insulin action has two components: impaired insulin secretion and decreased insulin sensitivity (insulin resistance) in organs on which insulin acts. Both are components of the pathogenesis of type 2 diabetes. In general, insulin resistance plays a key role causing type 2 diabetes in Caucasians, whereas impaired insulin secretion plays a key role in the development of type 2 diabetes in East Asians.

Several systematic reviews and meta-analyses have been conducted including an analysis to investigate the difference between ethnic groups in glucose lowering efficacy of dipeptidyl peptidase-4 (DPP-4) inhibitors. However, no consistent result has been found to date. Thus, in this first research, we performed a systematic review and meta-analysis of randomized controlled studies and conducted meta-regression analyses to assess the correlation between the glucose-lowering efficacy of DPP-4 inhibitors in patients with type 2 diabetes and potential factors including ethnicity of study subjects and study regions; in particular, Japanese were dealt separately from other Asians. The finding of the first research suggested that a higher baseline Hemoglobin A1c (HbA1c), studies in Japanese subjects, and studies conducted in Japan are factors of greater efficacy of DPP-4 inhibitors on weighted mean difference (WMD) in the change of HbA1c from baseline.

As for the sodium glucose co-transporter-2 (SGLT-2) inhibitor, systematic reviews and meta-analysis to investigate the difference in efficacy and safety of SGLT-2 inhibitors between different ethnic groups considering the pathophysiology has not been conducted so far. The reason might be its insulin independent mechanism of action.

Thus, as a secondary research, we performed a systematic review and meta-analysis of randomized controlled studies and conducted meta-regression analyses to assess the correlation between the glucose-lowering efficacy of SGLT-2 inhibitors in patients with type 2 diabetes and potential factors including ethnicity of study subjects and study regions. The finding of the second research suggested that higher fasting plasma glucose is a factor of greater efficacy of SGLT-2 inhibitors on WMD in the change of HbA1c from baseline.

Our finding suggests that paying attention to baseline HbA1c for DPP-4 inhibitors and baseline fasting plasma glucose for SGLT-2 inhibitors in planning and conducting clinical studies, and in comparing the data with other clinical studies is important. With regards to the ethnicity of study subjects, our finding indicates that differences in the contribution of the insulin secretory defect and the insulin resistance in the pathophysiology of type 2 diabetes between Asians and non-Asians do not affect the response to active oral hypoglycemic agents which have insulin independent mechanism.

In type 2 diabetes area, placebo effect has rarely been discussed. The third research focus, therefore, was to identify the factors that contribute to placebo effect in clinical studies for both DPP-4 inhibitor and SGLT-2 inhibitor by meta-regression analyses. The finding of the third research suggested that study conduct in Asia is a factor of larger HbA1c change from baseline in the placebo group. This differential HbA1c response in the placebo arm should be taken into consideration when comparing the data based on different clinical practice in each region. In the future, it is desirable to evaluate the influence of different study regions and/or subject ethnicity on efficacy and safety in multiregional studies.

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Abbreviations

BMI	body mass index
DPP-4	dipeptidyl peptidase-4
GFR	glomerular filtration rate
HbA1c	Hemoglobin A1c
JDS	Japan Diabetes Society
NGSP	National Glycohemoglobin Standardization Program
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SGLT-2	sodium glucose co-transporter-2
WMD	weighted mean difference

1. Introduction

Type 2 diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from lack of insulin action. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels

The prevalence of diabetes has recently been increasing worldwide [1-3]. The number of adults with diabetes was estimated to be 415 million in 2015 and is expected to rise to 642 million by 2040 [3]. East Asian countries have also seen a continuous increase in diabetes [2,3]. According to a 1997 survey in Japan [4], total of "individuals strongly suspected of having diabetes" and "individuals in whom diabetes cannot be ruled out" were approximately 13.7 million, which increased to 20.5 million in 2012 [5].

The mechanism for a lack of insulin action has two components: impaired insulin secretion and decreased insulin sensitivity (insulin resistance) in organs on which insulin acts [6]. Impaired insulin secretion is a condition in which enough insulin is not supplied to satisfy the adequate action on the organs. Insulin resistance refers to a condition in which the normal function of insulin in peripheral tissues does not occur. Both are components of the pathogenesis of type 2 diabetes. In general, insulin resistance plays a key role causing type 2 diabetes in Caucasians [7], whereas impaired insulin secretion plays the key role in the development of type 2 diabetes in East Asians [8-11]. Besides the differences in pathogenesis between ethnic groups, there are also differences at the individual level. In the case of impaired insulin secretion, excessive lipid uptake occurs even in mild obesity, and when a lifestyle that is deficient in exercise is superimposed on this, insulin resistance, and thus type 2 diabetes, is more likely to

occur.

In controlling type 2 diabetes, lifestyle management focusing on diet and exercise is carried out first, and in case the target value for glycemic control is not achieved, drug treatment is started. Seven oral hypoglycemic agents are divided into three modes of actions: insulin sensitizing agents, insulin secretagogues, and carbohydrate absorption/ excretion-modulating agent. Biguanides and thiazolidines are classified as insulin sensitizing agents, sulfonylureas, fast-acting insulin secretagogues and dipeptidyl peptidase-4 (DPP-4) inhibitors are insulin secretagogues, and α-glucosidase inhibitor and sodium glucose co-transporter-2 (SGLT-2) inhibitors are carbohydrate absorption/excretion-modulating agents. Pharmacotherapy will be selected depending on the patient's etiology and patho-physiological stages (states) considering different modes of actions of each drug.

There is no apparent difference among the regions e.g., the United States, European countries, and Japan, regarding diagnosis and drug treatment options for type 2 diabetes. Hemoglobin A1c (HbA1c) is widely used internationally as an important index in the treatment of diabetes and a primary endpoint of efficacy in clinical studies. Based on the background such as the differences in pathogenesis and so on, however, it has been considered in Japan that extrapolation of multinational clinical study results by bridging strategy and/or conducting multinational studies is difficult in the development of an oral hypoglycemic agent for type 2 diabetes patients.

Several systematic reviews and meta-analyses have been conducted so far including an analysis to investigate the difference between ethnic groups in glucose lowering efficacy of DPP-4 inhibitors. Kim et al. [15] reported improved glucose lowering efficacy in Asians compared with other ethnic groups, and Park et al. [16]

reported the difference between Japanese and non-Japanese patients in efficacy and safety. However there were several limitations in these analyses. First, the number of articles which deal with clinical studies in the Asian or Japanese population is few compared to that in the Western population. Second, seven Japanese studies referred in the above mentioned articles showed a greater reduction in HbA1c such as –1.67%, which is far greater than the generally recognized value such as –0.6 % to –0.9 %. Third, HbA1c as it had been expressed in Japan used the Japan Diabetes Society (JDS) system values and not the National Glycohemoglobin Standardization Program (NGSP) values. From April 1, 2013, the HbA1c results are reported using only the NGSP values and there is a possibility that meta-analysis in the above mentioned articles were conducted in different HbA1c values.

As for the SGLT-2 inhibitor, which appeared on the market most recently, a pooled analysis was conducted to assess the efficacy and safety in patients of different ethnicities, Hispanic/Latino and non-Hispanic/Latino [17]. But systematic reviews and meta-analysis to investigate the difference in efficacy and safety of SGLT-2 inhibitors between different ethnic groups considering the pathophysiology such as Asian and non-Asian or Japanese and non-Japanese like DPP-4 inhibitor has not been conducted so far. The reason might be its insulin independent mechanism of action.

The placebo phenomenon in chronic pain or neuropsychiatric disorder has been widely recognized in clinical research because high placebo responses were reported to be the cause of failure of clinical studies. In type 2 diabetes area, however, placebo effect has rarely been discussed.

Against this background, we performed a systematic review and meta-analysis of randomized controlled studies for type 2 diabetes and assessed the correlation

between the glucose-lowering efficacy of oral hypoglycemic agents and potential factors related to clinical study design and subject demographic, and conduct including the ethnicity of study subjects and study regions. As oral hypoglycemic agents, we selected two classes of mechanism of actions, a DPP-4 inhibitor, which has an insulin secretion mechanism (Research 1), and a SGLT-2 inhibitor, which has an insulin independent mechanism (Research 2). Additionally, we conducted an analysis to identify factors contributing to placebo effect in clinical studies for type 2 diabetes. Based on these analyses, we discuss the points to be considered in future clinical development of oral hypoglycemic drugs.

2. Research 1 (DPP-4 inhibitor)

2.1. Objectives

DPP-4 inhibitors are a class of oral hypoglycemic agents that inhibit the enzyme DPP-4. The enzyme breaks down the incretin gastrointestinal hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, which are released in response to a meal and stimulate glucose-dependent insulin secretion [12, 13]. DPP-4 inhibitors are now in widespread use in clinical practice including East Asian countries and are rapidly becoming first-line therapy [14].

The pathophysiological differences may have an impact on the therapeutic approach and several systematic reviews and meta-analyses have been conducted including an analysis to investigate the difference between ethnic groups in glucose lowering efficacy of DPP-4 inhibitors. Kim et al. [15] reported improved glucose lowering efficacy in Asians compared with other ethnic groups, and Park et al. [16] reported the difference between Japanese and non-Japanese patients in efficacy and safety. Others [18-20] have analyzed the correlation between glucose-lowering efficacy and baseline characteristics without including ethnic information. However, no consistent result has been found to date.

Thus, we performed a systematic review and meta-analysis of randomized controlled studies and conducted meta-regression analyses to assess the correlation between the glucose-lowering efficacy of DPP-4 inhibitors including alogliptin, linagliptin, sitagliptin, saxagliptin and vildagliptin in patients with type 2 diabetes and potential factors including ethnicity of study subjects and study regions; in particular, Japanese were dealt separately from other Asians.

2.2. Method

The study conduct and results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21].

2.2.1. Data sources and searches

A systematic search was performed to identify potentially relevant studies in Medline, Embase, Cochrane Central Register, Japan Medical Abstracts Society and ClinicalTrials.gov databases up to October 4, 2016. In addition, the search included the reviews of approved drugs from the US Food and Drug Administration (www.fda.gov), European Medicines Agency (www.ema.europa.eu) and Japanese Pharmaceuticals and Medical Devices Agency (www.pmda.go.jp). An extensive search for alogliptin, linagliptin, sitagliptin, saxagliptin and vildagliptin was performed.

Eligibility criteria for study selection included the following: (1) randomized controlled studies comparing a DPP-4 inhibitor with a placebo as either monotherapy or combination therapy with other oral glucose-lowering drugs in patients with type 2 diabetes, (2) studies with treatment duration of at least 12 weeks, (3) studies with information on HbA1c values of placebo-adjusted change from baseline, and (4) studies published or described in English or Japanese. Eligibility was assessed independently by two authors (K.F. and M.K.), and disagreements were resolved by consensus with another author (M.N.).

Exclusion criteria included the following: (1) studies with duration of less than 12 weeks because of inadequate time to assess HbA1c change, (2) duplicate and extended studies from original studies, and (3) studies lacking relevant information.

2.2.2. Data extraction

Two authors (K.F. and M.K.) independently conducted data extraction. Any disagreements were resolved by consensus with another author (M.N.). The following data were extracted from the eligible studies: study design (monotherapy or oral combination therapy), name of the first author, year of publication, country where the study was conducted, treatment regimen, study duration, number of participants, percentage of male, means of age, duration of diabetes, baseline HbA1c values, baseline fasting plasma glucose, baseline body mass index (BMI), baseline body weight, and percentages of Asians and Japanese subjects. The primary outcome was the effect of DPP-4 inhibitors on HbA1c change from baseline compared with placebo at each study's primary endpoint.

For dose-ranging studies, only data from currently approved medication doses were extracted. In the absence of such data, equivalent amounts of daily doses were used. If a study had two or three comparisons (one monotherapy arm and one or two combination therapy arms), each comparison was treated separately. When there was a comparison for different administration times in a day (morning vs. evening), both data were used. Some data not available in the original paper were subsequently extracted using information from a full report available in the study registry, ClinicalTrials.gov, or from reviews of approved drugs by regulatory agencies.

For ethnicity information, we followed the classification of 'Asian' used by the authors of each study. If a study did not disclose ethnic information but was conducted in Asian countries with a relatively homogeneous population, e.g., Korea, China, Japan or Taiwan, we assumed the study participants were Asian. In addition, if a study did not disclose ethnic information but was conducted only in Japan, we assumed the study

participants were Japanese.

In order to further explore potential differences in HbA1c-lowering efficacy among the ethnicity and study regions, we created three classifications, Type A, B and C. Type A and Type B focused on ethnicity of study subjects, and Type C focused on study regions. In Type A classification, Japanese was included in Asian, and we categorized the studies either as a "study in Asian subjects" or a "study in non-Asian subjects" based on whether the percentage of Asians was larger than or equal to 50% or not. In Type B, Japanese was dealt separately from Asian, and we divided the studies into three groups: a "study in Japanese subjects" that enrolled only Japanese, a "study in Asian subjects" that excluded the study in Japanese subjects from study in Asian subjects of Type A, and a "study in non-Asian subjects." In Type C, we divided the studies into three groups: a "study conducted in Japan" that conducted only in Japan, an "study conducted in Asia" conducted only in Asia and excluding those conducted only in Japan, and a "study conducted multinationally."

For HbA1c value, when the Japan Diabetes Society (JDS) values, HbA1c (JDS), were used in Japanese studies [22], then they were calculated into National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) using the formula HbA1c (%) = HbA1c (JDS) (%) + 0.4% and used in the present study.

2.2.3. Study quality and risk of bias assessment

The Jadad Scale was adopted to assess the quality of all included studies. We evaluated the included studies regarding randomization, concealment of allocation, double-blinding, withdrawals and dropouts. To assess publication bias, we used the funnel plot and Egger's test.

2.2.4. Statistical analysis

Weighted mean difference (WMD) and 95% confidence interval for HbA1c change from baseline in DPP-4 inhibitors compared with placebo was calculated. Heterogeneity between studies was assessed by using Q statistic and I^2 statistic. A *P*-value of Q statistic <0.10 and a value of 50% or greater of I^2 statistic was considered significant. A random-effect model was used because significant heterogeneity was reported in several meta-analyses [15,16]. Meta-regression was applied to investigate potential factors affecting the placebo adjusted HbA1c lowering efficacy. The pre-specified factors such as study duration, percentage of male, age, duration of diabetes, baseline HbA1c values, fasting plasma glucose, BMI, body weight, percentage of Asians and additional categorizations regarding ethnicity of study subjects and study regions were used in the meta-regression.

Univariate meta-regression was performed first to identify potential factors affecting the HbA1c-lowering efficacy of the DPP-4 inhibitor. Negative coefficient indicates efficacy is in favor of the factor. A significant association was defined as *P* <0.2 in univariate meta-regression. Factors were further analyzed by multivariate meta-regression. When correlation between explanatory variables was identified, one variable was selected to be included in the multivariate meta-regression. A statistically significant difference was defined as *P* <0.05 in the multivariate meta-regression. Analyses were performed using StatDirect version 2.7.9 (StatDirect Ltd., Altrincham, Cheshire, UK) and R software, version 3.2.0 [23].

2.3. Result

2.3.1. Literature search

We identified 2,721 potentially relevant articles from a literature search. Based

on the review of the abstracts, 72 studies met all of the inclusion criteria. Further 270 studies were identified in the ClinicalTrials.gov registry and among them 7 unpublished clinical studies were included in the analysis (Fig. 1). A total of 79 studies (Appendix: reference 1-79) with 91 arms and 25,095 patients were used for the analysis (Table 1). Regarding the factors related to ethnicity and regions, in Type B, 17 were studies in Asian subjects, 18 were studies in Japanese subjects and 41 were studies in non-Asian subjects. As for Type C, 6 were studies conducted in Asia, 18 were studies conducted in Japan and 55 were studies conducted multinationally (Table 2).

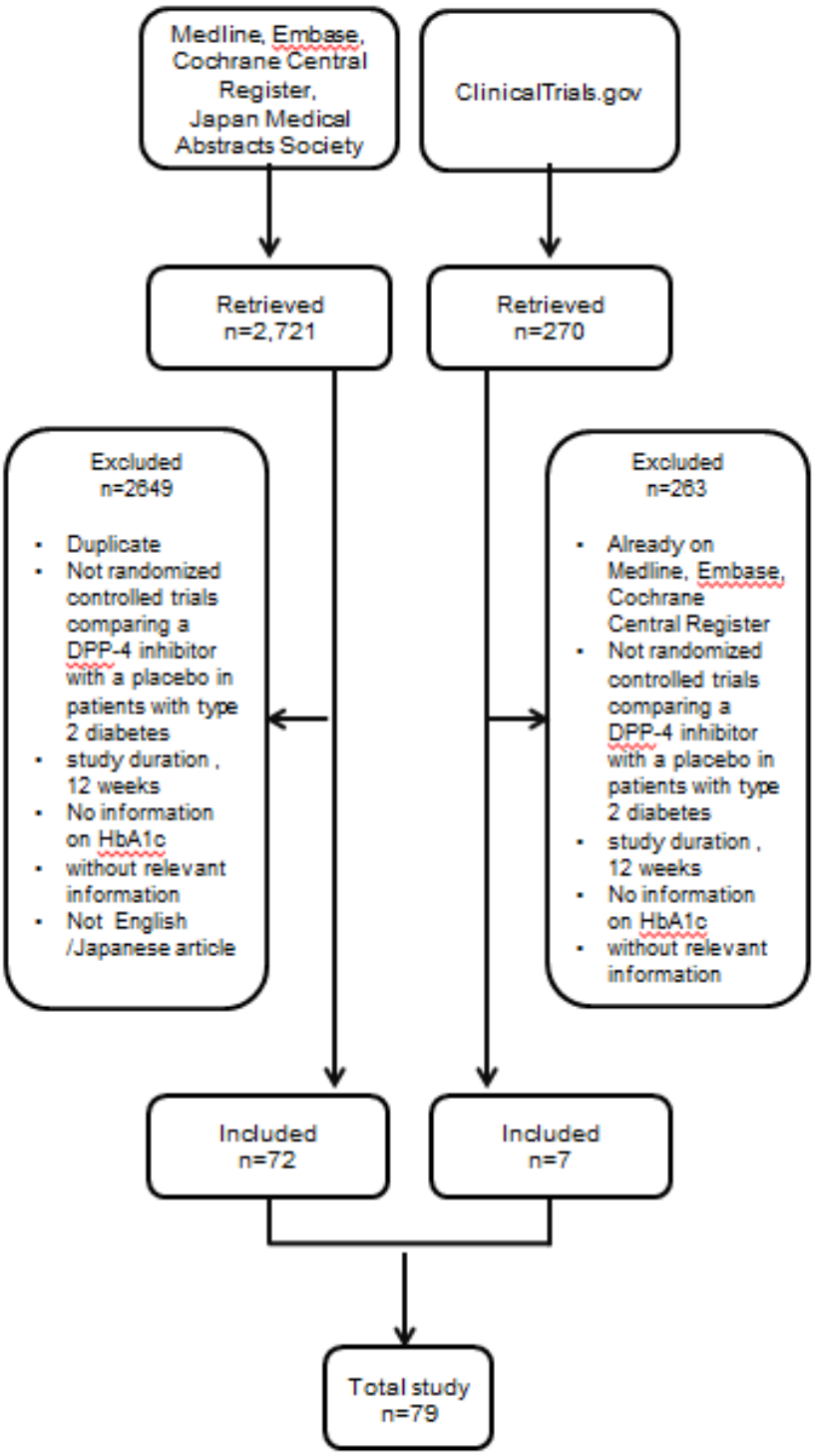

Figure 1 Flow diagram of study selection

Table 1 Studies included in the analysis

Source	Number of participants	Treatment duration (weeks)	DPP-4 inhibitors	background antidiabetic therapy	Age (years)	Baseline HbA1c (%)
DeFronzo, 2008[1]	196	26	Alogliptin 25 mg QD	none	53.4	8.0
Nauck , 2009[2]	314	26	Alogliptin 25 mg QD	metformin	54.7	7.9
Pratley, 2009[3]	296	26	Alogliptin 25 mg QD	pioglitazone	55.3	8.0
Pratley, 2009[4]	297	26	Alogliptin 25 mg QD	glyburide	56.7	8.1
Seino, 2011[5]	155	12	Alogliptin 25 mg QD	none	59.3	7.9
Kaku, 2011[6]	228	12	Alogliptin 25 mg QD	pioglitazone	59.7	7.9
Seino, 2011[7]	154	12	Alogliptin 25 mg QD	voglibose	62.6	8.0
Seino, 2012[8]	207	12	Alogliptin 25 mg QD	glimepiride	60.0	8.6
Seino, 2012[9]	196	12	Alogliptin 25 mg QD	metformin	52.2	8.0
Pan, 2016[10]_1[a]	185	16	Alogliptin 25 mg QD	none	52.4	8.0
Pan, 2016[10]_2[b]	197	16	Alogliptin 25 mg QD	metformin	53.1	8.0
Pan, 2016[10]_3[c]	124	16	Alogliptin 25 mg QD	pioglitazone (with or without metformin)	52.2	8.0
Forst, 2010[11]	137	12	Linagliptin 5 mg QD	metformin	59.9	8.4
Del Prato, 2011[12]	503	24	Linagliptin 5 mg QD	none	55.7	8.0
Taskinen, 2011[13]	700	24	Linagliptin 5 mg QD	metformin	56.5	8.1
Owens, 2011[14]	1055	24	Linagliptin 5 mg QD	metformin and sulfonylurea	58.1	8.1
Lewin, 2012[15]	245	18	Linagliptin 5 mg QD	sulfonylurea	56.9	8.6
Kawamori, 2012[16]	239	12	Linagliptin 5 mg QD	none	60.1	8.0

Source	Number of participants	Treatment duration (weeks)	DPP-4 inhibitors	background antidiabetic therapy	Age (years)	Baseline HbA1c (%)
Ross, 2012[17]_1[a]	268	12	Linagliptin 5 mg QD	metformin	58.6	8.0
Ross, 2012[17]_2[b]	267	12	Linagliptin 2.5 mg BID	metformin	58.9	8.0
Haak, 2012[18]	214	24	Linagliptin 5 mg QD	none	56.0	8.7
Barnett, 2012[19]	227	18	Linagliptin 5 mg QD	none	56.5	8.1
Bajaj, 2014[20]	278	24	Linagliptin 5 mg QD	metformin and pioglitazone	53.8	8.4
Chen, 2015[21]	301	24	Linagliptin 5 mg QD	none	54.4	8.0
Wang, 2016[22]	305	24	Linagliptin 5 mg QD	metformin	55.6	8.0
Rosenstock, 2008[23]	114	12	Saxagliptin 5 mg QD	none	54.6	8.0
Rosenstock, 2009[24]	201	24	Saxagliptin 5 mg QD	none	53.9	8.0
DeFronzo, 2009[25]	370	24	Saxagliptin 5 mg QD	metformin	54.7	8.1
Hollander, 2009[26]	370	24	Saxagliptin 5 mg QD	thiazolidinedione	53.6	8.3
Chacra, 2009[27]	520	24	Saxagliptin 5 mg QD	glyburide	55.0	8.4
Yang, 2011[28]	570	24	Saxagliptin 5 mg QD	metformin	54.1	7.9
Pan, 2012[29]	568	24	Saxagliptin 5 mg QD	none	51.4	8.2
Frederich, 2012[30]_1[a]	148	24	Saxagliptin 5 mg QD AM	none	55.1	7.9
Frederich, 2012[30]_2[b]	146	24	Saxagliptin 5 mg QD PM	none	55.3	7.9
White, 2014[31]	160	12	Saxagliptin 2.5 mg BID	metformin	55.4	7.9
Moses, 2014[32]	257	24	Saxagliptin 5 mg QD	metformin and sulfonylurea	57.0	8.3
Seino, 2014[33]_1[a]	168	12	Saxagliptin 5 mg QD	none	58.6	8.5
Seino, 2014[33]_2[b]	187	24	Saxagliptin 5 mg QD	none	57.9	8.0

Source	Number of participants	Treatment duration (weeks)	DPP-4 inhibitors	background antidiabetic therapy	Age (years)	Baseline HbA1c (%)
Matthaei、2015[34]	315	24	Saxagliptin 5 mg QD	dapagliflozin and metformin	54.6	7.9
NCT00918879[35]	213	24	Saxagliptin 5 mg QD	none	48.7	8.3
Ristic, 2005[36]	121	12	Vildagliptin 100 mg QD	none	55.4	7.7
Dejager, 2007[37]_1[a]	317	24	Vildagliptin 100 mg QD	none	52.9	8.4
Dejager, 2007[37]_2[b]	312	24	Vildagliptin 50 mg BID	none	52.5	8.5
Pi-Sunyer, 2007[38]_1[a]	183	24	Vildagliptin 100 mg QD	none	52.0	8.4
Pi-Sunyer, 2007[38]_2[b]	175	24	Vildagliptin 50 mg BID	none	51.1	8.5
Bosi, 2007[39]	367	24	Vildagliptin 100 mg QD	metformin	54.2	8.4
Garber, 2007[40]	316	24	Vildagliptin 100 mg QD	pioglitazone	54.4	8.7
Garber, 2008[41]	345	24	Vildagliptin 100 mg QD	glimepiride	58.0	8.5
Kikuchi, 2009[42]	148	12	Vildagliptin 50 mg BID	none	59.6	7.8
Kikuchi , 2010[43]	202	12	Vildagliptin 50 mg BID	glimepiride	59.7	8.3
Kikuchi, 2010[44]_1[a]	124	12	Vildagliptin 50 mg BID	none	59.5	7.7
Kikuchi, 2010[44]_2[b]	118	12	Vildagliptin 100 mg QD	none	61.1	7.7
Pan, 2012[45]	290	24	Vildagliptin 50 mg BID	metformin	54.3	8.0
Odawara, 2014[46]	139	12	Vildagliptin 50 mg BID	metformin	58.1	8.0
Raz, 2006[47]	315	18	Sitagliptin 100 mg QD	none	54.8	8.0
Aschner, 2006[48]	491	24	Sitagliptin 100 mg QD	none	53.9	8.0
Charbonnel, 2006[49]	701	24	Sitagliptin 100 mg QD	metformin	54.5	8.0
Rosenstock, 2006[50]	353	24	Sitagliptin 100 mg QD	pioglitazone	56.3	8.0

Source	Number of participants	Treatment duration (weeks)	DPP-4 inhibitors	background antidiabetic therapy	Age (years)	Baseline HbA1c (%)
Hanefeld, 2007[51]_1[a]	221	12	Sitagliptin 100 mg QD	none	55.9	7.7
Hanefeld, 2007[51]_2[b]	222	12	Sitagliptin 50 mg BID	none	55.6	7.7
Hanefeld, 2007[51]_3[c]	223	12	Sitagliptin 50 mg QD	none	55.9	7.6
Goldstein, 2007[52]	355	24	Sitagliptin 100 mg QD	none	53.4	8.8
Hermansen, 2007[53]_1[a]	212	24	Sitagliptin 100 mg QD	glimepiride	54.8	8.4
Hermansen, 2007[53]_2[b]	229	24	Sitagliptin 100 mg QD	glimepiride and metformin	57.1	8.3
Scott, 2007[54]	249	12	Sitagliptin 50 mg BID	none	55.2	7.9
Raz, 2008[55]	190	30	Sitagliptin 100 mg QD	metformin	54.8	9.2
Scott, 2008[56]	186	18	Sitagliptin 100 mg QD	metformin	55.2	7.8
Nonaka, 2008[57]	152	12	Sitagliptin 100 mg QD	none	55.3	8.0
Mohan, 2009[58]	530	18	Sitagliptin 100 mg QD	none	50.9	8.7
Iwamoto, 2010[59]_1[a]	143	12	Sitagliptin 100 mg QD	none	59.3	8.1
Iwamoto, 2010[59]_2[b]	145	12	Sitagliptin 50 mg QD	none	60.2	8.1
Kashiwagi, 2011[60]	134	12	Sitagliptin 50 mg QD	pioglitazone	58.4	8.1
Barzilai, 2011[61]	206	24	Sitagliptin 50 or 100 mg QD	none	71.9	7.8
Tajima, 2011[62]	138	12	Sitagliptin 50 mg QD	glimepiride	60.7	9.1
Yang, 2012[63]	395	24	Sitagliptin 100 mg QD	metformin	54.6	8.5
Nicolle, 2012[64]	130	12	Sitagliptin 100 mg QD	metformin	52.5	7.7
Fonseca, 2013[65]	313	26	Sitagliptin 100 mg QD	metformin and pioglitazone	56.0	8.8

Source	Number of participants	Treatment duration (weeks)	DPP-4 inhibitors	background antidiabetic therapy	Age (years)	Baseline HbA1c (%)
Dobs, 2013[66]	262	18	Sitagliptin 100 mg QD	metformin and rosiglitazone	54.5	8.8
Roden, 2013[67]	451	24	Sitagliptin 100 mg QD	none	55.0	7.9
Lavalle-González, 2013[68]	549	26	Sitagliptin 100 mg QD	metformin	55.4	7.9
Tajima, 2013[69]	133	12	Sitagliptin 50 mg QD	voglibose	60.5	7.9
Kadowaki, 2013[70]	149	12	Sitagliptin 50 mg QD	metformin	58.4	7.9
Amin, 2015[71]	112	12	Sitagliptin 100 mg QD	metformin	47.5	8.0
Ji, 2016[72]	247	24	Sitagliptin 100 mg QD	none	52.7	8.9
Moses, 2016[73]	422	24	Sitagliptin 100 mg QD	sulfonylurea and metformin	54.9	8.4
NCT01177384[74]	381	24	Sitagliptin 100 mg QD	acarbose	57.1	8.1
NCT01289990[75]	451	52	Sitagliptin 100 mg QD	none	55.0	7.9
NCT01338870[76]	100	12	Sitagliptin 100 mg QD	metformin	55.7	8.1
NCT01336738[77]	107	12	Sitagliptin 100 mg QD	metformin	56.7	8.3
NCT01590771[78]	498	24	Sitagliptin 100 mg QD	sulfonylurea with or without metformin	57.0	8.6
NCT01703221[79]	248	24	Sitagliptin 50 mg QD	none	60.3	NR

QD once-daily dosing, *BID* twice-daily dosing, *NR* not reported

[a] 1 represents the first pair of the article

[b] 2 represents the second pair of the article

[c] 3 represents the third pair of the article

Table 2 Three classifications for studies

Type A	Study in non-Asian subjects 41 studies	Study in Asian subjects 35 studies	
Type B	Study in non-Asian subjects 41 studies	Study in Asian subjects (excluding the Japanese) 17 studies	Study in Japanese subjects [a] 18 studies
Type C	Study conducted multinationally 55 studies	Study conducted in Asia (excluding Japan) 6 studies	Study conducted in Japan [a] 18 studies

[a] Studies classified as "Study in Japanese subjects" (Type B) and "Study conducted in Japan" (Type C) were the same.

2.3.2. Quality of included studies and publication bias

The Jaded score was 3.74, and we determined the quality of included studies was high. The funnel plot of WMD for HbA1c and standard error in 79 studies is shown in Fig. 2. Funnel plot asymmetry was assessed using Egger's test and it indicated that there was no publication bias (p = 0.067). The I^2 statistic test for heterogeneity was 69.7%, and the value of Q statistic was significant.

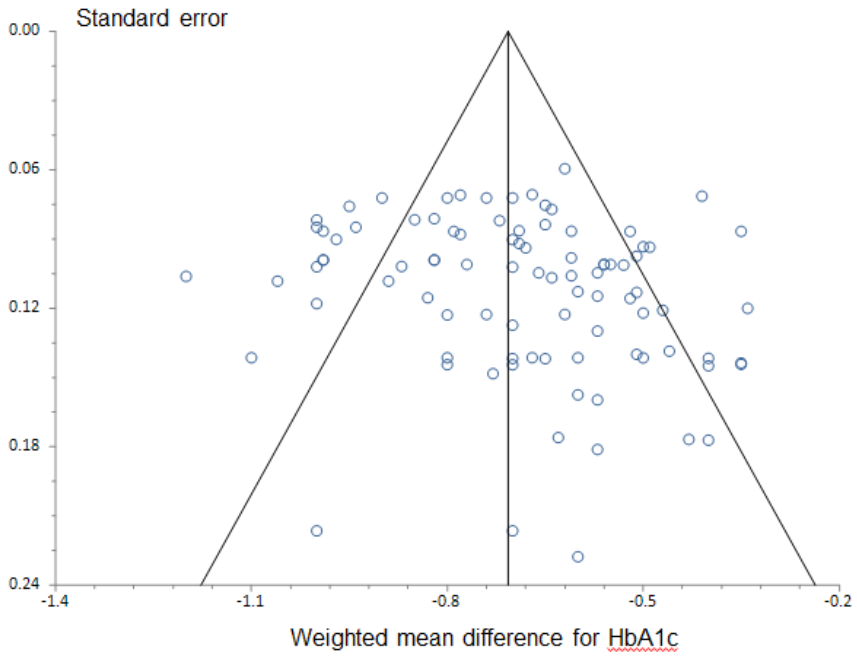

Figure 2 Funnel plot of weighted mean difference for HbA1c and standard error

2.3.3. Primary outcome

HbA1c data for 91 arms from 79 studies were pooled. The difference of HbA1c between the DPP-4 inhibitor group and placebo group was −0.695% (95% CI −0.734 to −0.656).

2.3.4. Univariate meta-regression

Univariate meta-regression showed relations between the WMD in the change of HbA1c from baseline value and several factors such as study duration (coefficient=0.009, p = 0.001), percentage of male (−0.009, p <0.001), age (−0.024, p <0.001), duration of diabetes (−0.034, p =0.001), baseline HbA1c values (−0.087, p = 0.162), BMI (0.029, p <0.001), body weight (0.009, p <0.001) and percentage of Asians (−0.002, p <0.001). Additionally, studies in Asian subjects in Type A (−0.129, p = 0.001), studies in Japanese subjects in Type B (−0.254, p <0.001), and studies conducted in Japan in Type C (−0.263, p <0.001) showed relations in each of the analyses. Because BMI and body weight correlated with the percentage of Asians, we excluded BMI and body weight from the multivariate meta-regression, and used the three classifications (Type A, B and C).

2.3.5. Multivariate meta-regression

The factors significantly associated with the WMD in the change of HbA1c from baseline using univariate meta-regression were further analyzed by multivariate meta-regression (Table 3). Baseline HbA1c was identified as a common influencing factor in all the analyses using the three types of classifications. Also, study in Japanese subjects in Type B and study conducted in Japan in Type C were identified as influencing factors.

Table 3 Results of multivariate meta-regression analysis

Factors	Estimate	95% CI	*P*-value
a. Multivariate meta-regression with Type A			
Study duration (week)	0.007	(-0.003, 0.016)	0.166
Male (%)	-0.003	(-0.010, 0.004)	0.392
Age (years)	-0.011	(-0.027, 0.004)	0.138
Duration of diabetes (years)	-0.012	(-0.034, 0.011)	0.302
Baseline HbA1c (%)	-0.169	(-0.300, -0.037)	0.012
Study in Asian subjects	-0.078	(-0.176, 0.019)	0.116
b. Multivariate meta-regression with Type B			
Study duration (week)	0.003	(-0.006, 0.013)	0.502
Male (%)	0.001	(-0.006, 0.008)	0.684
Age (years)	-0.002	(-0.018, 0.013)	0.777
Duration of diabetes (years)	-0.007	(-0.029, 0.014)	0.499
Baseline HbA1c (%)	-0.157	(-0.281, -0.032)	0.014
Study in Asian subjects	0.018	(-0.096, 0.132)	0.755
Study in Japanese subjects	- 0.242	(-0.389, -0.095)	0.001
c. Multivariate meta-regression with Type C			
Study duration (week)	0.003	(-0.007, 0.012)	0.588
Male (%)	0.001	(-0.006, 0.008)	0.710
Age (years)	-0.004	(-0.019, 0.011)	0.605
Duration of diabetes (years)	-0.008	(-0.029, 0.014)	0.484
Baseline HbA1c (%)	-0.157	(-0.281, -0.032)	0.013
Study conducted in Asia	0.011	(-0.129, 0.152)	0.873
Study conducted in Japan	- 0.243	(-0.391, -0.096)	0.001

Type A, the studies were divided into 2 groups; a “study in Asian subjects” or a “study in non-Asian subjects”

Type B, the studies were divided into 3 groups; a “study in Asian subjects”, a “study in Japanese subjects” or a “study in non-Asian subjects.”

Type C, the studies were divided into three groups: a “study conducted in Asia”, a “study conducted in Japan” or a “study conducted multinationally.”

HbA1c hemoglobin A1c

2.4. Discussion

We performed meta-regression analyses to identify the factors influencing the glucose-lowering efficacy of DPP-4 inhibitors by analyzing 79 studies with 91 arms and 25,095 patients. We found WMD in the placebo-adjusted change of HbA1c from baseline was −0.695%, which is consistent with the previously reported meta-analyses ranging between −0.6% and −0.72%.

Using univariate meta-regression, factors such as study duration, percentage of male, age, duration of diabetes, baseline HbA1c values, BMI, body weight and percentage of Asians were identified to be correlated with WMD in the change of HbA1c from baseline. The results of study duration, percentage of male, age, duration of diabetes, BMI, and percentage of Asians were in agreement with the analysis conducted by Kim et al [15]. Additionally, in the present study, relations were shown in studies in Asian subjects in the classification Type A, studies in Japanese subjects in Type B and studies conducted in Japan in Type C. Based on these results, DPP-4 inhibitors exhibit a better glucose-lowering efficacy with shorter study duration, in older patients, with longer duration of diabetes, with higher baseline HbA1c, with lower BMI and body weight, and with a higher percentage of Asians. A better glucose lowering efficacy was also shown in studies in Asian subjects, studies in Japanese subjects and studies conducted in Japan.

Multivariate meta-regression showed a better glucose lowering efficacy with high baseline HbA1c, suggesting baseline HbA1c is a robust factor. Moreover, studies in Japanese subjects in Type B and studies conducted in Japan in Type C were factors influencing the glucose-lowering efficacy of DPP-4 inhibitors.

Bloomgarden et al. [24] reported that the baseline glycemic status of patients

recruited into clinical studies strongly influences the reduction of HbA1c following pharmacologic intervention with the five major anti-hyperglycemic oral agent classes. The authors concluded that clinical investigators and study sponsors should consider these findings when testing the effectiveness of new anti-hyperglycemic agents. A higher baseline HbA1c would be a predictor of a greater HbA1c reduction with the use of DPP-4 inhibitors [20, 25]. However, the HbA1c value used by Esposito et al. [20] and Deacon [25] in their analysis was different from our study; they used the absolute HbA1c reduction without taking into account the placebo effect. In the present study, we found that a higher baseline HbA1c is a factor of greater efficacy of DPP-4 inhibitors on WMD in the change of HbA1c from baseline. For clinical studies, the comparison with placebo is generally required. Therefore, in evaluating the efficacy of DPP-4 inhibitors in clinical development, it is important to provide the information on factors that influence the efficacy of DPP-4 inhibitors. Our finding suggests that paying attention to baseline HbA1c in planning and conducting of clinical studies, and comparing the data with other studies is important.

In the present study, we used three classifications regarding ethnicity of study subjects and study regions to explore potential differences among them. In the classification Type A, Japan was included in Asia. In Type B and C, we distinguished between Asia and Japan focusing on ethnicity in Type B and on regions in Type C. Studies in Japanese subjects and studies conducted in Japan are factors affecting the efficacy of DPP-4 inhibitors. However, studies in Asian subjects in Type B and studies conducted in Asia in Type C are not associated. This finding differs from those by Kim et al. [15], who reported that the DPP-4 inhibitors exhibit a better glucose-lowering efficacy in Asians than in other ethnic groups. Our finding indicates that differences in

the contribution of the insulin secretory defect and insulin resistance in the pathophysiology of type 2 diabetes between Asians and non-Asians does not significantly affect the response to DPP-4 inhibitors and does not explain the mechanism underlying the difference in the response.

The differences in the efficacy of DPP-4 inhibitors between Japanese and non-Japanese patients have been reported. Interestingly, Park et al. [16] suggested that the difference in characteristics such as age, duration of diabetes, baseline HbA1c and BMI between Japanese and non-Japanese patients could provide some explanation for the discrepancy in clinical studies. In their analysis, however, they did not clearly mention whether they took into consideration the difference of HbA1c values between JDS and NGSP. In our study, if an investigation in Japan did not mention the value of HbA1c (%), we checked the documents, review reports or other sources in order to use HbA1c (NGSP) equivalent values (%) for the analysis. The mean baseline HbA1c values were not significantly different among studies in non-Asian subjects, studies in Asian subjects and studies in Japanese subjects (data not shown), and the baseline HbA1c was an independent factor associated with the efficacy of DPP-4 inhibitors in our study.

When we looked at the placebo response in the classification Type B and Type C, the trend of the response was different among the three groups. Placebo response was increased in studies in Japanese subjects and studies conducted in Japan, whereas it decreased in studies in Asian subjects and studies conducted in Asia; in studies in non-Asian subjects and studies conducted multinationally it showed minimal change from baseline (data not shown). Further investigation is needed for better understanding the reason for the difference. In the present study, the factors analyzed in the univariate

meta-regression do not clearly explain the difference in efficacy of the DPP4-inhibitor in studies in Japanese subjects/studies conducted in Japan.

Our analysis indicates that studies in Japanese subjects /studies conducted in Japan as well as the baseline HbA1c values are associated with the efficacy of DPP-4 inhibitors. This result should be taken into account when planning and conducting clinical studies. Further investigation is needed to understand the association of the differences in the contribution of insulin secretory defect and insulin resistance in the pathophysiology of type 2 diabetes among ethnicity with the glucose-lowering efficacy of DPP-4 inhibitors.

3. Research 2 (SGLT-2 inhibitor)

3.1. Objectives

Most recently approved oral hypoglycemic drugs with a new mechanism is SGLT2 inhibitors. Inhibition of SGLT-2 decreases reabsorption of glucose in proximal renal tubular cells, leading to an increase in urinary glucose excretion and a reduction in plasma glucose levels. SGLT-2 inhibitors entered the Japanese market in 2014. Canagliflozin, dapagliflozin, and empagliflozin have been approved for use in the Unites States, the European Union and Japan, while ipragliflozin, luseogliflozin, and tofogliflozin have been approved for use only in Japan.

A pooled analysis was conducted to assess the efficacy and safety in patients of different ethnicities by Davidson et al. [17]. They reported that the SGLT2 inhibitor canagliflozin is equally effective and generally well-tolerated in both Hispanic/Latino and non-Hispanic/Latino. They focused on this ethnicity because Hispanic/Latino patients are one of the large populations with type 2 diabetes in the United States. But systematic reviews and meta-analysis to investigate the difference in efficacy and safety of SGLT-2 inhibitors between different ethnic groups considering the pathophysiology such as Asian and non-Asian or Japanese and non-Japanese like DPP-4 inhibitor has not been conducted so far. The reason might be its insulin independent mechanism of action, neither insulin secretion nor sensitization.

Thus, we performed a systematic review and meta-analysis of randomized controlled studies and conducted meta-regression analyses to assess the correlation between the glucose-lowering efficacy of SGLT-2 inhibitors including dapagliflozin, canagliflozin and empabliflozin in patients with type 2 diabetes and potential factors including ethnicity of study subjects and study regions; in particular, Japanese were

dealt separately from other Asians.

3.2. Method

The study conduct and results were reported in accordance with the PRISMA statement [21].

3.2.1. Data sources and searches

A systematic search was performed to identify potentially relevant studies in Medline, Embase, Cochrane Central Register, Japan Medical Abstracts Society and ClinicalTrials.gov databases up to December 31, 2015. In addition, the search included the reviews of approved drugs from the US Food and Drug Administration (www.fda.gov), European Medicines Agency (www.ema.europa.eu) and Japanese Pharmaceuticals and Medical Devices Agency (www.pmda.go.jp). An extensive search for dapagliflozin, canagliflozin and empagliflozin was performed.

Eligibility criteria for study selection included the following: (1) randomized controlled studies comparing aSGLT-2 inhibitor with a placebo as either monotherapy or combination therapy with other oral glucose-lowering drugs in patients with type 2 diabetes, (2) studies with treatment duration of at least 12 weeks, (3) studies with information on HbA1c values of placebo-adjusted change from baseline, and (4) studies published or described in English or Japanese. Eligibility was assessed independently by two authors (K.F. and M.K.), and disagreements were resolved by consensus with another author (M.N.).

Exclusion criteria included the following: (1) studies with duration of less than 12 weeks because of inadequate time to assess HbA1c change, (2) duplicate and

extended studies from original studies, and (3) studies lacking relevant information.

3.2.2. Data extraction

Two authors (K.F. and M.K.) independently conducted data extraction. Any disagreements were resolved by consensus with another author (M.N.). The following data were extracted from the eligible studies: study design (monotherapy or oral combination therapy), name of the first author, year of publication, country where the study was conducted, treatment regimen, study duration, number of participants, percentage of male, means of age, duration of diabetes, baseline HbA1c values, baseline fasting plasma glucose, BMI, baseline body weight, and percentages of Asians and Japanese subjects. The primary outcome was the effect of SGLT-2 inhibitors on HbA1c change from baseline compared with placebo at each study's primary endpoint.

For dose-ranging studies, only data from currently approved medication doses were extracted. In the absence of such data, equivalent amounts of daily doses were used. If a study had two or three comparisons (one monotherapy arm and one or two combination therapy arms), each comparison was treated separately. When there was a comparison for different administration times in a day (morning vs. evening), both data were used. Some data not available in the original paper were subsequently extracted using information from a full report available in the study registry, ClinicalTrials.gov, or from reviews of approved drugs by regulatory agencies.

For ethnicity information, we followed the classification of 'Asian' used by the authors of each study. If a study did not disclose ethnic information but was conducted in Asian countries with a relatively homogeneous population, e.g., Korea, China, Japan or Taiwan, we assumed the study participants were Asian. In addition, if a study did not

disclose ethnic information but was conducted only in Japan, we assumed the study participants were Japanese.

In order to further explore potential differences in HbA1c-lowering efficacy among the ethnicity and study regions, we created three classifications, Type A, B and C. Type A and Type B focused on ethnicity of study subjects, and Type C focused on study regions. In Type A classification, Japanese was included in Asian, and we categorized the studies either as a "study in Asian subjects" or a "study in non-Asian subjects" based on whether the percentage of Asians was larger than or equal to 50% or not. In Type B, Japanese was dealt separately from Asian, and we divided the studies into three groups: a "study in Japanese subjects" that enrolled only Japanese, a "study in Asian subjects" that excluded the study in Japanese subjects from study in Asian subjects of Type A, and a "study in non-Asian subjects." In Type C, we divided the studies into three groups: a "study conducted in Japan" that conducted only in Japan, an "study conducted in Asia" conducted only in Asia and excluding those conducted only in Japan, and a "study conducted multinationally."

For HbA1c value, when the JDS values, HbA1c (JDS), were used in Japanese studies [22], then they were calculated into NGSP equivalent value (%) using the formula HbA1c (%) = HbA1c (JDS) (%) + 0.4% and used in the present study.

3.2.3. Study quality and risk of bias assessment

The Jadad Scale was adopted to assess the quality of all included studies. We evaluated the included studies regarding randomization, concealment of allocation, double-blinding, withdrawals and dropouts. To assess publication bias, we used the funnel plot and Egger's test.

3.2.4. Statistical analysis

WMD and 95% confidence interval for HbA1c change from baseline in SGLT-2 inhibitors compared with placebo was calculated. Heterogeneity between studies was assessed by using Q statistic and I^2 statistic. A *P*-value of Q statistic <0.10 and a value of 50% or greater of I^2 statistic was considered significant. A random-effect model was used because significant heterogeneity was reported in several meta-analyses [26, 27]. Meta-regression was applied to investigate potential factors affecting the placebo adjusted HbA1c lowering efficacy. The pre-specified factors such as study duration, percentage of male, age, duration of diabetes, baseline HbA1c values, fasting plasma glucose, BMI, body weight, percentage of Asians and additional categorizations regarding ethnicity of study subjects and study regions were used in the meta-regression.

Univariate meta-regression was performed first to identify potential factors affecting the HbA1c-lowering efficacy of the SGLT-2 inhibitor. Negative coefficient indicates efficacy is in favor of the factor. A significant association was defined as *P* <0.2 in univariate meta-regression. Factors were further analyzed by multivariate meta-regression. When correlation between explanatory variables was identified, one variable was selected to be included in the multivariate meta-regression. A statistically significant difference was defined as *P* <0.05 in the multivariate meta-regression. Analyses were performed using StatDirect version 2.7.9 (StatDirect Ltd., Altrincham, Cheshire, UK) and R software, version 3.2.0 [23].

3.3. Result

3.3.1. Literature search

We identified 496 potentially relevant articles from a literature search. Based on the review of the abstracts, 29 studies met all of the inclusion criteria. Further 83 studies were identified in the ClinicalTrials.gov registry and among them 1 unpublished clinical study was included in the analysis (Fig. 3). A total of 30 studies (Appendix 2: 1-33) with 75 arms and 20,170 patients were used for the analysis (Table 4). Regarding the factors related to ethnicity and regions, in Type B, 6 were studies in Asian subjects, 5 were studies in Japanese subjects and 20 were studies in non-Asian subjects. As for Type C, 2 were studies conducted in Asia, 5 were studies conducted in Japan and 24 were studies conducted multinationally (Table 5).

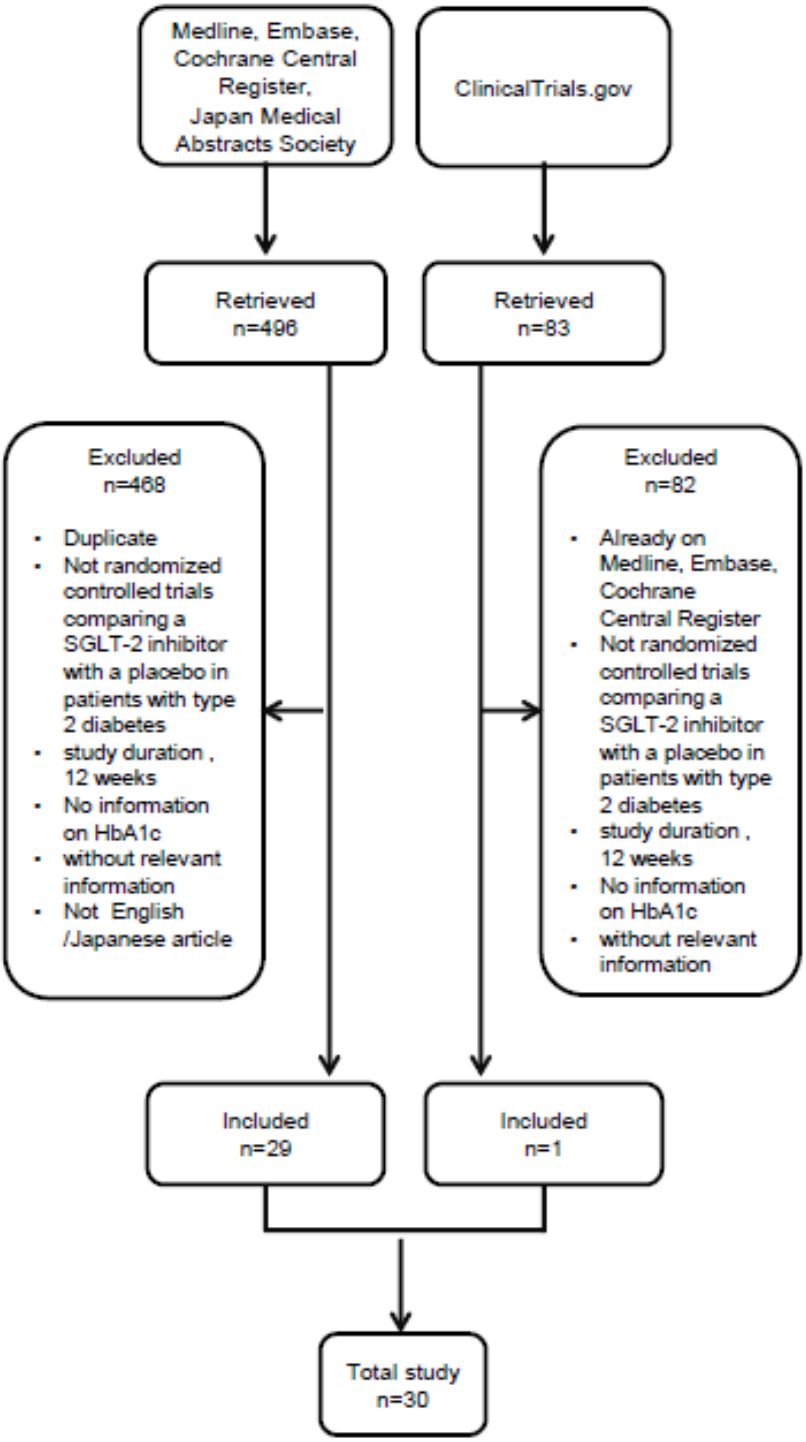

Figure 3 Flow diagram of study selection

Table 4 Studies included in the analysis

Source	Number of participants	Treatment duration (weeks)	SGLT-2 inhibitors	background antidiabetic therapy	Age (years)	Baseline HbA1c (%)	BL FPG (mg/dl)
List, 2009[1]	112	12	Dapagliflozin 5 mg QD	none	54.0	8.0	151.6
List, 2009[1]	101	12	Dapagliflozin 10 mg QD	none	53.5	8.0	149.1
Bailey, 2010[2]	274	24	Dapagliflozin 5 mg QD	metformin	54.0	8.1	167.2
Bailey, 2010[2]	272	24	Dapagliflozin 10 mg QD	metformin	53.2	8.0	160.7
Ferrannini, 2010[3]_1[a]	139	24	Dapagliflozin 5 mg QD AM	none	52.7	7.9	161.0
Ferrannini, 2010[3]_1[a]	145	24	Dapagliflozin 10 mg QD AM	none	51.7	7.9	163.1
Ferrannini, 2010[3]_2[b]	135	24	Dapagliflozin 5 mg QD PM	none	53.6	7.8	158.4
Ferrannini, 2010[3]_2[b]	143	24	Dapagliflozin 10 mg QD PM	none	51.6	7.9	164.3
Strojek, 2011[4]	287	24	Dapagliflozin 5 mg QD	glimepiride	60.3	8.1	173.3
Strojek, 2011[4]	296	24	Dapagliflozin 10 mg QD	glimepiride	59.6	8.1	172.2
Biley, 2012[5]	136	24	Dapagliflozin 5 mg QD	none	52.4	7.9	159.2
Rosenstock, 2012[6]	280	24	Dapagliflozin 5 mg QD	pioglitazone	53.3	8.4	164.7
Rosenstock, 2012[6]	279	24	Dapagliflozin 10 mg QD	pioglitazone	53.7	8.4	162.8
Kaku, 2013[7]	112	12	Dapagliflozin 5 mg QD	none	58.2	8.1	161.8
Kaku, 2013[7]	106	12	Dapagliflozin 10 mg QD	none	57.5	8.2	161.1

Source	Number of participants	Treatment duration (weeks)	SGLT-2 inhibitors	background antidiabetic therapy	Age (years)	Baseline HbA1c (%)	BL FPG (mg/dl)
Jabbour, 2014[8]	221	24	Dapagliflozin 10 mg QD	sitagliptin	53.0	8.1	159.4
Jabbour, 2014[8]	226	24	Dapagliflozin 10 mg QD	sitagliptin and metformin	56.7	7.9	165.8
Kaku, 2014[9]	173	24	Dapagliflozin 5 mg QD	none	59.5	7.5	138.6
Kaku, 2014[9]	175	24	Dapagliflozin 10 mg QD	none	58.9	7.5	139.2
Ji, 2014[10]	260	24	Dapagliflozin 5 mg QD	none	51.4	8.3	160.8
Ji, 2014[10]	265	24	Dapagliflozin 10 mg QD	none	50.6	8.3	164.7
Matthaei, 2015[11]	218	24	Dapagliflozin 10 mg QD	sulfonylurea and metformin	61.0	8.2	173.8
Schumm-Draeger, 2015[12]	201	16	Dapagliflozin 2.5 mg BID	metformin	58.4	7.9	155.4
Schumm-Draeger, 2015[12]	200	16	Dapagliflozin 5 mg BID	metformin	56.9	7.9	156.4
NCT00736879[13]	136	24	Dapagliflozin 5 mg QD	none	52.4	7.9	159.2
Rosenstock, 2012[14]	129	12	Canagliflozin 100 mg QD	metformin	52.5	7.8	166.0
Rosenstock, 2012[14]	130	12	Canagliflozin 200 mg QD	metformin	53.1	7.7	162.0
Rosenstock, 2012[14]	129	12	Canagliflozin 300 mg QD	metformin	52.8	7.7	161.5
Wilding, 2013[15]	313	26	Canagliflozin 100 mg QD	sulfonylurea and metformin	57.1	8.1	171.0
Wilding, 2013[15]	312	26	Canagliflozin 300 mg QD	sulfonylurea and metformin	56.5	8.1	168.3
Inagaki, 2013[16]	149	12	Canagliflozin 100 mg QD	none	57.7	8.0	165.9
Inagaki, 2013[16]	151	12	Canagliflozin 200 mg QD	none	57.3	8.1	168.3
Inagaki, 2013[16]	150	12	Canagliflozin 300 mg QD	none	57.4	8.1	169.9

Source	Number of participants	Treatment duration (weeks)	SGLT-2 inhibitors	background antidiabetic therapy	Age (years)	Baseline HbA1c (%)	BL FPG (mg/dl)
Lavalle-Gonzalez, 2013[17]	551	26	Canagliflozin 100 mg QD	metformin	55.4	7.9	166.2
Lavalle-Gonzalez, 2013[17]	550	26	Canagliflozin 300 mg QD	metformin	55.3	7.9	169.8
Stenlof, 2013[18]	387	26	Canagliflozin 100 mg QD	none	55.4	8.1	170.1
Stenlof, 2013[18]	389	26	Canagliflozin 300 mg QD	none	55.5	8.0	170.1
Forst, 2014[19]	228	26	Canagliflozin 100 mg QD	pioglitazone and metformin	57.5	8.0	166.5
Forst, 2014[19]	229	26	Canagliflozin 300 mg QD	pioglitazone and metformin	57.7	8.0	163.8
Inagaki, 2014[20]	183	24	Canagliflozin 100 mg QD	none	58.3	8.0	160.4
Inagaki, 2014[20]	182	24	Canagliflozin 200 mg QD	none	57.8	8.0	164.1
Qiu, 2014[21]	186	18	Canagliflozin 50 mg BID	metformin	57.8	7.7	162.0
Qiu, 2014[21]	186	18	Canagliflozin 150 mg BID	metformin	56.9	7.7	162.9
Ji, 2015[22]_1[a]	449	18	Canagliflozin 100 mg QD	metformin (with or without sulfonylurea)	56.1	7.9	157.5
Ji, 2015[22]_1[a]	453	18	Canagliflozin 300 mg QD	metformin (with or without sulfonylurea)	56.1	8.0	159.3
Ji, 2015[22]_2[b]	218	18	Canagliflozin 100 mg QD	metformin	54.7	7.9	158.4
Ji, 2015[22]_2[b]	222	18	Canagliflozin 300 mg QD	metformin	55.3	8.0	158.4
Ji, 2015[22]_3[c]	231	18	Canagliflozin 100 mg QD	sulfonylurea and metformin	57.6	7.9	155.7

Source	Number of participants	Treatment duration (weeks)	SGLT-2 inhibitors	background antidiabetic therapy	Age (years)	Baseline HbA1c (%)	BL FPG (mg/dl)
Ji, 2015[22]_3[c]	231	18	Canagliflozin 300 mg QD	sulfonylurea and metformin	57.0	8.0	160.2
Haring, 2013[23]	450	24	Empagliflozin 10 mg QD	sulfonylurea and metformin	57.0	8.1	151.2
Haring, 2013[23]	441	24	Empagliflozin 25 mg QD	sulfonylurea and metformin	57.1	8.1	153.9
Roden, 2013[24]	452	24	Empagliflozin 10 mg QD	none	55.5	7.9	153.6
Roden, 2013[24]	452	24	Empagliflozin 25 mg QD	none	54.4	7.9	153.5
Rosenstock, 2013[25]	142	12	Empagliflozin 10 mg QD	metformin	59.5	8.0	173.5
Rosenstock, 2013[25]	141	12	Empagliflozin 25 mg QD	metformin	59.5	8.0	177.0
Ferrannini, 2013[26]	163	12	Empagliflozin 10 mg QD	none	57.8	7.9	174.6
Ferrannini, 2013[26]	164	12	Empagliflozin 25 mg QD	none	57.0	7.8	171.0
Kovacs, 2014[27]	330	24	Empagliflozin 10 mg QD	pioglitazone (with or without metformin)	54.7	8.2	151.8
Kovacs, 2014[27]	333	24	Empagliflozin 25 mg QD	pioglitazone (with or without metformin)	54.4	8.2	151.7
Haring, 2014[28]	424	24	Empagliflozin 10 mg QD	metformin	55.7	7.9	155.1
Haring, 2014[28]	421	24	Empagliflozin 25 mg QD	metformin	55.8	7.9	152.5
Kadowaki, 2014[29]	218	12	Empagliflozin 10 mg QD	none	58.3	7.9	156.6
Kadowaki, 2014[29]	218	12	Empagliflozin 25 mg QD	none	58.0	8.0	156.2
Ross, 2015[30]	322	16	Empagliflozin 12.5 mg BID	metformin	57.7	7.8	157.8
Ross, 2015[30]	321	16	Empagliflozin 25 mg QD	metformin	58.1	7.7	159.0

Source	Number of participants	Treatment duration (weeks)	SGLT-2 inhibitors	background antidiabetic therapy	Age (years)	Baseline HbA1c (%)	BL FPG (mg/dl)
Ross, 2015[30]	322	16	Empagliflozin 5 mg BID	metformin	58.5	7.8	161.4
Ross, 2015[30]	321	16	Empagliflozin 10 mg QD	metformin	58.3	7.8	161.4
Roden, 2015[31]	452	76	Empagliflozin 10 mg QD	none	55.5	7.9	153.9
Roden, 2015[31]	452	76	Empagliflozin 25 mg QD	none	54.4	7.9	153.9
Haering, 2015[32]	450	76	Empagliflozin 10 mg QD	sulfonylurea and metformin	57.0	8.1	151.2
Haering, 2015[32]	441	76	Empagliflozin 25 mg QD	sulfonylurea and metformin	57.1	8.1	153.9
NCT01289990[33]_1[a]	424	76	Empagliflozin 10 mg QD	metformin	55.7	7.9	155.1
NCT01289990[33]_1[a]	421	76	Empagliflozin 25 mg QD	metformin	55.8	7.9	152.5
NCT01289990[33]_2[b]	331	76	Empagliflozin 10 mg QD	pioglitazon	55.0	NR	NR
NCT01289990[33]_2[b]	334	76	Empagliflozin 25 mg QD	pioglitazon	55.1	NR	NR

QD once-daily dosing, *BID* twice-daily dosing, *NR* not reported

[a] 1 represents the first pair of the article

[b] 2 represents the second pair of the article

[c] 3 represents the third pair of the article

Table 5 Three classifications for studies

Type A	Study in non-Asian subjects 19 studies	Study in Asian subjects 11 studies	
Type B	Study in non-Asian subjects 20 studies	Study in Asian subjects (excluding the Japanese) 6 studies	Study in Japanese subjects [a] 5 studies
Type C	Study conducted multinationally 24 studies	Study conducted in Asia (excluding Japan) 2 studies	Study conducted in Japan [a] 5 studies

[a] Studies classified as "Study in Japanese subjects" (Type B) and "Study conducted in Japan" (Type C) were the same.

3.3.2. Quality of included studies and publication bias

The Jaded score was 3.90, and we determined the quality of included studies was high. The funnel plot of WMD for HbA1c and standard error in 30 studies is shown in Fig. 4. Funnel plot asymmetry was assessed using Egger's test and it indicated that there was no publication bias ($p = 0.117$). The I^2 statistic test for heterogeneity was 76.2%, and the value of Q statistic was significant.

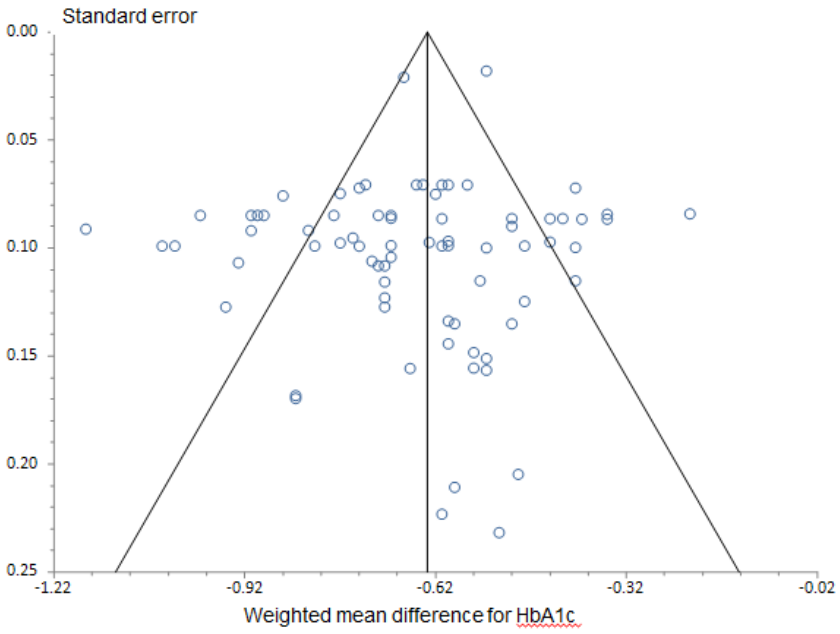

Figure 4 Funnel plot of weighted mean difference for HbA1c and standard error

3.3.3. Primary outcome

HbA1c data for 75 arms from 30 studies were pooled. The difference of HbA1c between the SGLT-2 inhibitor group and placebo group was −0.657% (95% CI −0.696 to −0.617).

3.3.4. Univariate meta-regression

Univariate meta-regression showed relations between the WMD in the change of HbA1c from baseline value and several factors such as study design (coefficient=0.201, $p<0.001$), percentage of male (−0.009, $p<0.001$), baseline HbA1c values (−0.087, $p = 0.162$), baseline fasting plasma glucose (−0.006, $p = 0.020$), BMI (0.015, $p = 0.081$), body weight (0.003, $p = 0.180$) and percentage of Asians (−0.001, $p = 0.011$). Additionally, studies in Asian subjects in Type A (−0.103, $p = 0.016$), studies in Japanese subjects in Type B (−0.200, $p = 0.001$), and studies conducted in Japan in Type C (−0.178, $p =0.002$) showed relations in each of the analyses. Because BMI and body weight correlated with the percentage of Asians, we excluded BMI and body weight from the multivariate meta-regression, and used the three classifications (Type A, B and C). Furthermore, study design correlated with the three classifications, we exclude study design from multivariate meta-regression.

3.3.5. Multivariate meta-regression

The factors significantly associated with the WMD in the change of HbA1c from baseline using univariate meta-regression were further analyzed by multivariate meta-regression (Table 6). Baseline fasting plasma glucose was identified as a common influencing factor in all the analyses using the three types of classifications. Also, percentage of male in Type A, and percentage of male and baseline HbA1c were identified as influencing factors, respectively.

Table 6 Results of multivariate meta-regression analysis

Factors	Estimate	95% CI	*P*-value
a. Multivariate meta-regression with Type A			
Male (%)	-0.007	(-0.012, -0.002)	0.008
Baseline HbA1c (%)	-0.111	(-0.357, 0.136)	0.378
Baseline fasting plasma glucose (mg/dl)	-0.009	(-0.015, -0.003)	0.003
Study in Asian subjects	-0.097	(-0.200, 0.006)	0.066
b. Multivariate meta-regression with Type B			
Male (%)	-0.005	(-0.011, 0.002)	0.142
Baseline HbA1c (%)	-0.138	(-0.394, 0.118)	0.292
Baseline fasting plasma glucose (mg/dl)	-0.009	(-0.015, -0.003)	0.005
Study in Asian subjects	-0.086	(-0.193, 0.021)	0.114
Study in Japanese subjects	-0.149	(-0.315, 0.016)	0.077
c. Multivariate meta-regression with Type C			
Male (%)	-0.007	(-0.014, 0.000)	0.036
Baseline HbA1c (%)	-0.237	(-0.470, -0.004)	0.046
Baseline fasting plasma glucose (mg/dl)	-0.006	(-0.011, -0.001)	0.029
Study conducted in Asia	0.070	(-0.044, 0.185)	0.227
Study conducted in Japan	-0.063	(-0.222, 0.096)	0.435

Type A, the studies were divided into 2 groups; a “study in Asian subjects” or a “study in non-Asian subjects”

Type B, the studies were divided into 3 groups; a “study in Asian subjects”, a “study in Japanese subjects” or a “study in non-Asian subjects.”

Type C, the studies were divided into three groups: a “study conducted in Asia”, a “study conducted in Japan” or a “study conducted multinationally.”

HbA1c hemoglobin A1c

3.4. Discussion

We performed meta-regression analyses to identify the factors influencing the glucose-lowering efficacy of SGLT-2 inhibitors by analyzing 30 studies with 75 arms

and 20,170 patients. We found WMD in the placebo-adjusted change of HbA1c from baseline was −0.66 %, which is consistent with the previously reported meta-analyses ranging between −0.455% and −0.78%.

Using univariate meta-regression, factors such as percentage of male, baseline HbA1c values, baseline fasting plasma glucose, BMI, body weight and percentage of Asians were identified to be correlated with WMD in the change of HbA1c from baseline. The results of baseline HbA1c values, baseline fasting plasma glucose and BMI were in agreement with the analysis conducted by Monami et al. [27]. Additionally, in the present study, relations were shown in studies in Asian subjects in the classification Type A, studies in Japanese subjects in Type B and studies conducted in Japan in Type C. Based on these results, SGLT-2 inhibitors exhibit a better glucose-lowering efficacy with higher baseline HbA1c, higher fasting glucose, with lower BMI and body weight, and with a higher percentage of Asians. A better glucose lowering efficacy was also shown in studies in Asian subjects, studies in Japanese subjects and studies conducted in Japan.

Multivariate meta-regression showed a better glucose lowering efficacy with high baseline fasting plasma glucose, suggesting baseline fasting plasma glucose is a robust factor. Additional categorizations regarding ethnicity of study subjects and study regions were not identified as an influencing factor of glucose-lowering efficacy of SGLT-2 inhibitors.

Ferrannini et al. [28] concluded SGLT-2 inhibitor induced glycosuria could be described as a dual function of the glomerular filtration rate (GFR) and plasma glucose levels with a coefficient of determination of 65% (or a multiple r =0.74) . This may explain our findings that higher baseline fasting plasma glucose is a factor of greater

efficacy of SGLT-2 inhibitors on WMD in the change of HbA1c from baseline. Because GFR was assessed in a few clinical studies, we did not include GFR as a pre-specified factor. Our finding suggests that paying attention to baseline fasting plasma glucose in planning and conducting of clinical studies, and in comparing the data with other studies is important.

We used three classifications regarding ethnicity of study subjects and study regions to explore potential differences among them. In the classification Type A, Japan was included in Asia. In Type B and C, we distinguished between Asia and Japan focusing on ethnicity in Type B and on regions in Type C. Any factors of these classifications were not identified as an influencing factor of glucose-lowering efficacy of SGLT-2 inhibitors. Our finding indicates that differences in the contribution of the insulin secretory defect and insulin resistance in the pathophysiology of type 2 diabetes between Asians and non-Asians do not affect the response to SGLT-2 inhibitors. The reason could be explained by its insulin independent mechanism of action, neither insulin secretion nor sensitization.

Our analysis indicates that the baseline fasting plasma glucose is associated with the efficacy of SGLT-2 inhibitors. This result should be taken into account when planning and conducting clinical studies, and comparing the data with other clinical studies.

4. Research 3 (Placebo effect)

4.1. Objectives

Through our research 1 and 2, different placebo phenomenon was observed among study regions. For example, high placebo responses were observed in study conducted in Asia and low placebo responses were observed in study conducted in Japan. This placebo phenomenon showed same trend in both the DPP -4 inhibitor and the SGLT-2 inhibitor studies.

The placebo phenomenon in chronic pain or neuropsychiatric disorder has been widely recognized in clinical research because high placebo responses were reported to be the cause of failure of clinical studies. In type 2 diabetes area, however, placebo effect has rarely been discussed.

Thus, we conducted meta-regression analyses to assess the factors that contributing to placebo effect in clinical studies for both DPP-4 inhibitor and SGLT-2 inhibitor. Potential factors including ethnicity of study subjects and study regions; in particular, Japanese were dealt separately from other Asians.

4.2. Method

4.2.1. Data sources, searches and extraction

We used the eligible studies identified in research 1 and research 2. The primary outcome was HbA1c change from baseline in placebo group at each study's primary endpoint.

In order to further explore potential differences in HbA1c change from baseline in placebo group among the ethnicity and study regions, we used two classifications, Type B and C, described in method of research 1 and research 2.

4.2.2. Statistical analysis

Meta-regression was applied to investigate potential factors affecting the HbA1c change from baseline in placebo group of each DPP-4 inhibitor and SGLT-2 inhibitor study. The pre-specified factors such as study duration, percentage of male, age, duration of diabetes, baseline HbA1c values, fasting plasma glucose, BMI, body weight, percentage of Asians and additional categorizations regarding ethnicity of study subjects and study regions were used in the meta-regression.

Same method was applied for univariate and multivariate meta-regression analyses as in research 1 and 2. Analyses were performed using StatDirect version 2.7.9 (StatDirect Ltd., Altrincham, Cheshire, UK) and R software, version 3.2.0 [23].

4.3. Result

4.3.1. Literature search

DPP-4 inhibitor study

A total of 79 studies (Appendix 1; reference 1-79) with 86 arms and 10,561 patients were used for the analysis (Table 1). Regarding the factors related to ethnicity and regions, in Type B, 17 were studies in Asian subjects, 18 were studies in Japanese subjects and 41 were studies in non-Asian subjects. As for Type C, 6 were studies conducted in Asia, 18 were studies conducted in Japan and 55 were studies conducted multinationally (Table 2).

SGLT-2 inhibitor study

A total of 30 studies (Appendix 2: 1-33) with 38 arms and 4,904 patients were

used for the analysis (Table 4). Regarding the factors related to ethnicity and regions, in Type B, 6 were studies in Asian subjects, 5 were studies in Japanese subjects and 20 were studies in non-Asian subjects. As for Type C, 2 were studies conducted in Asia, 5 were studies conducted in Japan and 24 were studies conducted multinationally (Table 5).

4.3.2. Univariate meta-regression

DPP-4 inhibitor study

Univariate meta-regression showed relations between the HbA1c change from baseline in placebo group and several factors such as study design (coefficient=-0.112, p = 0.030), study duration (−0.007, p = 0.052), percentage of male (0.007, p =0.007), age (0.031, p <0.001), duration of diabetes (0.031, p =0.015), BMI (−0.012, p =0.174) and body weight (−0.005, p =0.173). Additionally, studies in Japanese subjects (0.198, p <0.001) and studies in Asian subjects (−0.173, p =0.002) in Type B, and studies conducted in Japan (0.228, p <0.001) and studies conducted in Asia (−0.259, p =0.001) in Type C showed relations in each of the analyses. Because BMI and body weight correlated with the percentage of Asians, we excluded BMI and body weight from the multivariate meta-regression, and used the two classifications (Type B and C).

SGLT-2 inhibitor study

Univariate meta-regression showed relations between the HbA1c change from baseline in placebo group and several factors such as study design (coefficient=−0.119, p = 0.001), percentage of male (0.008, p =0.024), age (0.025, p =0.051) and percentage of Asians (0.001, p =0.163). Additionally, studies in Japanese subjects in Type B (0.316,

p <0.001), and studies conducted in Japan (0.292, p <0.001) and studies conducted in Asia (−0.299, p =0.001) in Type C showed relations in each of the analyses.

4.3.3. Multivariate meta-regression

DPP-4 inhibitor study

The factors significantly associated with the HbA1c change from baseline in placebo group using univariate meta-regression were further analyzed by multivariate meta-regression (Table 7). Study design and duration of diabetes were identified as a common influencing factor in the both analyses using the two types of classifications. Also, study in Asian subjects in Type B and study conducted in Asia in Type C were identified as influencing factors.

Table 7 Results of multivariate meta-regression analysis (*DPP-4 inhibitor study*)

Factors	Estimate	95% CI	*P*-value
a. Multivariate meta-regression with Type B			
Study design (mono/combination)	-0.192	(-0.356, -0.027)	0.022
Study duration (week)	-0.004	(-0.018, 0.010)	0.571
Male (%)	0.001	(-0.007, 0.009)	0.820
Age (years)	-0.005	(-0.028, 0.018)	0.643
Duration of diabetes (years)	0.046	(0.003, 0.089)	0.036
Study in Asian subjects	-0.185	(-0.336, -0.034)	0.017
Study in Japanese subjects	0.104	(-0.078, 0.286)	0.261
b. Multivariate meta-regression with Type C			
Study design (mono/combination)	-0.202	(-0.362, -0.043)	0.013
Study duration (week)	-0.004	(-0.018, 0.009)	0.542
Male (%)	0.001	(-0.007, 0.009)	0.834
Age (years)	-0.002	(-0.025, 0.020)	0.845
Duration of diabetes (years)	0.049	(0.007, 0.091)	0.021
Study conducted in Asia	-0.235	(-0.414, -0.056)	0.010
Study conducted in Japan	0.099	(-0.082, -0.279)	0.284

Type B, the studies were divided into 3 groups; a "study in Asian subjects", a "study in Japanese subjects" or a "study in non-Asian subjects."

Type C, the studies were divided into three groups: a "study conducted in Asia", a "study conducted in Japan" or a "study conducted multinationally."

HbA1c hemoglobin A1c

SGLT-2 inhibitor study

The factors significantly associated with the HbA1c change from baseline in placebo group using univariate meta-regression were further analyzed by multivariate meta-regression (Table 8). Study design was identified as a common influencing factor in the both analyses using the two types of classifications. Also, age with type B and study conducted in Asia in Type C was identified as influencing factors.

Table 8 Results of multivariate meta-regression analysis (*SGLT-2 inhibitor study*)

Factors	Estimate	95% CI	*P*-value
a. Multivariate meta-regression with Type B			
Study design (mono/combination)	-0.236	(-0.380, -0.092)	0.001
Male (%)	0.000	(-0.009, 0.008)	0.923
Age	0.035	(0.007, 0.062)	0.013
Study in Asian subjects	0.000	(-0.128, 0.128)	0.998
Study in Japanese subjects	0.083	(-0.192, 0.358)	0.553
b. Multivariate meta-regression with Type C			
Study design (mono/combination)	-0.211	(-0.339, -0.083)	0.001
Male (%)	0.003	(-0.005, 0.012)	0.435
Age	0.025	(0.000, 0.050)	0.052
Study conducted in Asia	-0.262	(-0.048, -0.076)	0.006
Study conducted in Japan	0.032	(-0.213, 0.276)	0.798

Type B, the studies were divided into 3 groups; a "study in Asian subjects", a "study in Japanese subjects" or a "study in non-Asian subjects."

Type C, the studies were divided into three groups: a "study conducted in Asia", a "study conducted in Japan" or a "study conducted multinationally."

HbA1c hemoglobin A1c

4.4. Discussion

In the present study, we conducted analysis of placebo effect in clinical studies for DPP-4 inhibitors and SGLT-2 inhibitors. Multivariate meta-regression showed a larger HbA1c change from baseline in placebo group in the studies conducted in Asia for the both analyses, suggesting studies conducted in Asia is a robust factor. In other words, larger placebo response, improvement in the placebo group, was shown in studies conducted in Asia. This result was in agreement with what we found in our research 1 and 2.

He et al. [29] conducted meta-analysis and reported that HbA1c in the placebo arm declined by 0.26 % in the studies of DPP-4 inhibitors conducted in patients with

type 2 diabetes in China, whereas the placebo effect of those conducted outside China was close to 0. The authors concluded that there were significant differences in response in the placebo group of DPP-4 studies conducted in China and those conducted outside of China. In our research, China was the main region in the studies in Asia. Our findings were in agreement with those by He et al. [29], not only for DPP-4 studies but also for SGLT-2 studies, and supported their consideration of the reason for a large placebo effect; the significant benefit to participate in clinical study for subjects in China, obtaining more resource of medical care, could cause a bias and obvious impact on management of diabetes, and thus cause better blood glucose control even in placebo arm in China.

Although there was no statistical difference, coefficients of studies in Japanese subjects in Type B and studies conducted in Japan in Type C were positive and had the least influence on placebo effect. This is thought to be due to the adequate management in the medical practice in Japan, which causes less impact on placebo arm.

5. Overall Discussion

In order to discuss the points to be considered in future clinical development of oral hypoglycemic drug, three types of research were conducted.

The finding of the first research suggested that a higher baseline HbA1c is a factor of greater efficacy of DPP-4 inhibitors on WMD in the change of HbA1c from baseline. A higher baseline HbA1c has been reported to be a predictor of a greater HbA1c reduction with the use of DPP-4 inhibitors [20, 25]. However, the HbA1c value used by Esposito et al. [20] and Deacon [25] in their analysis was different from our study; they used absolute HbA1c reduction without taking into account the placebo effect. We used the WMD in the change of HbA1c in multivariate meta-regression and the analysis showed a better glucose lowering efficacy with high baseline HbA1c, suggesting baseline HbA1c is a robust factor.

Second, studies in Japanese subjects and studies conducted in Japan are factors affecting the efficacy of DPP-4 inhibitors. However, studies in Asian subjects and studies conducted in Asia are not associated, which means the efficacy of DPP-4 inhibitors shows no apparent difference between studies in Asian subjects and studies in non-Asian subject, or studies conducted in Asian and studies conducted multinationally. This finding differs from those by Kim et al. [15], who reported that the DPP-4 inhibitors exhibit a better glucose-lowering efficacy in Asians than in other ethnic groups. Our finding indicates that differences in the contribution of the insulin secretory defect and the insulin resistance in the pathophysiology of type 2 diabetes between Asians and non-Asians do not significantly affect the response to DPP-4 inhibitors and it does not explain the mechanism underlying the difference in the response.

The finding of the second research suggested that a higher baseline fasting

plasma glucose is a factor of greater efficacy of SGLT-2 inhibitors on WMD in the change of HbA1c from baseline. It was based on the multivariate meta-regression, suggesting baseline fasting plasma glucose is a robust factor. This finding is in agreement of the research by Monami et al. [27], though they employed a univariate meta-regression analysis. Our findings may be explained by the fact that glycosuria and plasma glucose levels have a strong positive correlation.

We used three classifications regarding ethnicity of study subjects and study regions to explore potential differences among them. However, no factors of these classifications were identified as an influencing factor of glucose-lowering efficacy of SGLT-2 inhibitors. Our finding indicates that differences in the contribution of the insulin secretory defect and the insulin resistance in the pathophysiology of type 2 diabetes between Asians and non-Asians does not affect the response to SGLT-2 inhibitors. The reason could be explain by its insulin independent mechanism of action, neither insulin secretion nor sensitization.

The finding of the third research suggested that studies conducted in Asia is a factor of larger HbA1c change from baseline in the placebo group. He et al. [29] reported that there were significant differences in response in the placebo group between DPP-4 studies conducted in China and those conducted outside of China. In our research, China was the main region in studies conducted in Asia. Given that our findings were in agreement with those by He et al. [29], not only for DPP-4 studies but also for SGLT-2 studies and supported their consideration of the reason for this high placebo effect; the significant benefit to participate in clinical study for subjects in China, obtaining more resource of medical care, could cause a bias and obvious impact on management of diabetes, and thus cause better blood glucose control even in placebo

arm in China.

Publication bias may exist and have imposed some limitations on our study. Another limitation is that we used summary data and not individual patient-level data. Furthermore, we included South Asians in the studies in Asian subjects, which mainly consisted of East Asians, because it was not possible to distinguish in some studies whether Asians included South Asians or not. The Asian population is also ethnically heterogeneous and has different demographic characteristics [30].

6. Conclusion

Paying attention to baseline HbA1c for DPP-4 inhibitors and baseline fasting plasma glucose for SGLT-2 inhibitors in planning and conducting clinical studies, and in comparing the data with other clinical studies is important. With regards to the ethnicity of study subjects, our finding indicates that differences in the contribution of the insulin secretory defect and the insulin resistance in the pathophysiology of type 2 diabetes between Asians and non-Asians do not affect the response to active oral hypoglycemic agents which have insulin independent mechanism. On the other hand, placebo effect was shown to be different among the subject ethnicity and/or study region. This differential HbA1c response in the placebo arm should be taken into consideration when comparing the data based on different clinical practice in each region. In the future, it is desirable to evaluate the influence of different study regions and/or subject ethnicity on efficacy and safety in multiregional studies.

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Appendix 1

1. DeFronzo RA, Fleck PR, Wilson CA, Mekki Q, Alogliptin Study G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control: a randomized, double-blind, placebo-controlled study. Diabetes Care. 2008;31(12):2315-7. doi:10.2337/dc08-1035.
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Appendix 2

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