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Characteristics of subjects with type 2 diabetes enrolled in randomized controlled trials and non-randomized controlled trials in Japan: A systematic review

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ABSTRACT

Aims/Introduction: This study aimed to understand the characteristics of type 2 diabetes subjects enrolled in randomized controlled trials (RCTs) and non-RCTs according to therapeutic regimens through systematic literature review.

Materials and Methods: PubMed and the database of the Japanese Medical Abstract Society (ICHUSHI) were searched for studies published from 2010 to 2019 reporting the efficacy and safety of glucose-lowering drugs in Japanese individuals with suboptimally controlled type 2 diabetes, and therapeutic regimens, demographics and clinical characteristics at the baseline were extracted. We evaluated the treatment arms, not the placebo arms.

Results: The literature searches identified 2,656 publications, 145 of which met all eligibility criteria and included 282 eligible arms. In the past 10 years, dipeptidyl peptidase-4 inhibitor was the most frequently studied in both RCTs and non-RCTs. Regarding the characteristics of enrolled subjects, sodium–glucose cotransporter 2 inhibitor and glucagon-like peptide-1 receptor agonist have been studied more in relatively obese subjects, and insulin has been studied in higher proportion of subjects with disease duration ≥10 years. Most of the RCTs included subjects aged 55–64 years, whereas a higher proportion of dipeptidyl peptidase-4 inhibitor and insulin arms in the non-RCTs included those aged ≥65 years. Dipeptidyl peptidase-4 inhibitor and sodium–glucose cotransporter 2 inhibitor were evaluated in subjects with no abnormalities in blood pressure or lipid parameters; however, only a few reports of those parameters have been assessed with glucagon-like peptide-1 receptor agonist and insulin.

Conclusions: As RCTs and non-RCTs differ in the baseline characteristics of type 2 diabetes subjects, it is necessary to integrate and evaluate both to understand the actual treatment status of type 2 diabetes.

INTRODUCTION

Type 2 diabetes is a chronic, progressive metabolic syndrome, characterized by hyperglycemia. Long periods of hyperglycemia increase the risk of microvascular complications, such as retinopathy, nephropathy and neurological disorders. Type 2 diabetes is also associated with arteriosclerosis, which can cause coronary artery disease, stroke and peripheral artery disease. Acute complications, such as diabetic ketoacidosis, might result in impaired consciousness, coma and eventually death[1]. The prevalence of diabetes in the global population aged 20–79 years was estimated to be 9.3% in 2019[2]. By 2030, it could reach 11.8%[3]. In Japan, 18.7% of men and 9.3% of women aged >20 years are strongly suspected to have diabetes[4].

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Treatment of type 2 diabetes is based initially on exercise and diet therapy. If blood glucose control remains suboptimal, oral glucose-lowering drugs (OGLDs), injectable drugs or a combination of these therapies are started in a stepwise manner[1]. The mean hemoglobin A1c (HbA1c) of Japanese people with type 2 diabetes is reported to be 7.1%[5]; that is, slightly above the general target for glycemic control (<7.0%)[1]. However, individuals with type 2 diabetes receiving injectable drugs have higher HbA1c at injectable drug initiation than those with OGLDs. The percentages of individuals with HbA1c of <7.0% are 27.8% on glucagon-like peptide 1 receptor agonists (GLP-1RA), 32.7% on insulins and 51.2% on OGLDs only[5].

Hyperglycemia and hypoglycemia often lead to significant medical expenses and productivity loss, causing a high social burden. Improving glycemic control in individuals with type 2 diabetes is one of the important treatment goals for clinicians. To achieve them, we need to further understand the patient characteristics, treatment regimens and unmet needs in suboptimally controlled type 2 diabetes by the type of treatment initiation in Japan, given that they reflect insights on how to improve the type 2 diabetes treatment.

Several systematic reviews report individual treatment regimens and improvement of treatment through behavioral interventions in subjects with suboptimally controlled type 2 diabetes[6–15]. However, only a few have comprehensively evaluated the status of study designs; that is, randomized controlled trials (RCTs) or non-RCTs, treatments, and characteristics of the subjects over several years. Therefore, the present systematic review aimed to further understand the trend of characteristics of the subjects with type 2 diabetes enrolled by type of treatment and study design.

MATERIALS AND METHODS

Protocol

The protocol was prepared in accordance with the Preferred Reporting Items in Systematic Reviews and Meta-analyses (PRISMA) statement[16] and PRISMA for systematic review protocols (PRISMA-P) statement[17]. It was registered at the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42020170888).

Study selection

We searched for studies in PubMed and the abstract database of the Japanese Medical Abstract Society (ICHUSHI). To identify studies on type 2 diabetes drugs in individuals with suboptimally controlled type 2 diabetes who have received one or more glucose-lowering drugs from the literatures published in Japanese or English from 2010 to 2019, we applied the eligibility criteria shown in Table 1. The literature searches in PubMed and ICHUSHI were carried out with the search terms shown in Tables S1 and S2, respectively. To acquire further information on the main outcomes that could not be obtained from the extracted articles, we carried out a targeted literature review in the quality of life database of the Niigata University of Health.

After removing duplicates, two independent reviewers (ZG and AS) selected eligible publications in a two-step manner. In

Table 1 | Eligibility criteria in this review

Type of studies	RCT and non-RCT, such as cohort studies, and case-controlled studies carried out in Japan (case reports, case series, *ex vivo* studies and animal studies were excluded)
Type of participants	Japanese individuals with type 2 diabetes, aged ≥18 years old, with HbA1c of ≥7.0%, treated with OADs, basal insulins, GLP-1RA or their combination therapies (individuals with type 1 diabetes mellitus, gestational diabetes mellitus and pediatric diabetes mellitus were excluded)
Type of interventions	Following regimens prescribed to control type 2 diabetes: a. Dose increase of an OAD or addition of a new OAD (OADs include biguanide, thiazolidine, sulfonyl urea, glinide, DPP-4i, α-glucosidase inhibitor and SGLT-2i) b. GLP-1RA c. Insulin therapy (basal, premixed, basal–bolus, addition of bolus insulin to basal insulin or addition of basal insulin to bolus insulin) d. Addition of insulin therapy to baseline therapy with GLP-1RA or OGLDs, or addition of GLP-1RA or OGLDs to baseline therapy with insulin
Type of comparison	One of the above interventions is treated as a comparator. However, some cohort studies do not have a comparator
Type of outcome	If none of following outcomes is reported, the study is excluded a. Efficacy (blood glucose, HbA1c, GLP-1 concentration, LDL-C, HDL-C, TG, SBP, DBP, bodyweight and BMI) b. Safety (AEs including complications [such as hypoglycemia], their incidence rate and time to the onset) c. QOL (EQ-5D/ SF-36/ SF-6D/ HUI/ TTO / SG/ DTSQ)
Year of publication	From 2010 to 2019

AE, adverse event; BMI, body mass index; DBP, diastolic blood pressure; DPP-4i, dipeptidyl peptidase-4 inhibitors; DTSQ, Diabetes Satisfaction Questionnaire; EQ-5D, EuroQol 5 Dimension; GLP-1RA, glucagon-like peptide-1 receptor agonists; HDL-C, high-density lipoprotein cholesterol; HUI, Health Utilities Index; LDL-C, low-density lipoprotein cholesterol; non-RCT, non-randomized controlled trial; OGLD, oral glucose-lowering drug; QOL, quality of life; RCT, randomized controlled trial; SF-36, Short Form (36) Health Survey; SF-6D, Short Form-6 Dimensions; SG, standard gamble; SGLT-2i, sodium–glucose cotransporter 2 inhibitors; SBP, systolic blood pressure; TG, triglyceride; TTO, time trade-off.

the primary screening, the reviewers screened the titles and abstracts against the eligibility criteria (Table 1). They retained all studies that could not be clearly excluded. In the secondary screening, they examined the full publications of the studies to determine whether they met eligibility criteria. Publications that had not been peer-reviewed were also excluded. Disagreement between the reviewers was resolved through discussions or participation of a third party.

Data extraction and management

The two reviewers (ZG and AS) extracted the following information about each of the studies: publication details (authors, journal name, title, year of publication), study details (study type and design, regimens, end-points, inclusion and exclusion criteria, numbers of included subjects per arm), subject details (age, sex, type 2 diabetes disease duration in years), baseline clinical characteristics (bodyweight, body mass index [BMI], blood glucose [fasting, post-prandial], HbA1c, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), quality of life, safety (the number or incidence of adverse events [AEs]), and adherence. Values of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides reported in mmol/L were converted to mg/dL. The number or incidence of AEs was extracted irrespective of types and severities. We identified studied regimens for type 2 diabetes treatments regardless of whether the regimens were case or control arms, and our data analysis was based on these studied regimens. Therefore, information on placebo arms was not collected.

When a given study was reported in multiple publications; for example, post-hoc analysis, subgroup analysis and results of continuation phases, the reviewers analyzed and summarized the data from all the publications. If they found any inconsistencies between the various publications on the same study, they discussed them and jointly decided how to proceed. We did not assess the risk of bias, because we targeted a wide variety of study designs.

Statistical analysis

For each arm, we defined the studied regimen as the regimen applied at the start of each study. When any glucose-lowering drugs were added to the baseline regimen of an arm, we identified only the added drugs as the studied regimen. Monotherapies and combination therapies were divided.

To understand the comprehensive trend of studies, we included all comparative studies. RCTs were expected to show different characteristics from non-RCTs, as most of them are highly controlled to evaluate the efficacy and safety of interventions, such as compounds with new mechanisms of actions before their approvals. Therefore, we classified and summarized the included arms by their study design as RCTs and non-RCTs.

We summarized the number of arms by study design and publication years to understand the trends. Furthermore, we examined the distribution of baseline age, BMI and disease duration to better understand the characteristics of Japanese people with type 2 diabetes. Then, we carried out subgroup analysis and summarized the changes in the number of arms by regimens with major classes; that is, insulin, GLP-1RA, dipeptidyl peptidase-4 inhibitors (DPP-4i) and sodium– glucose cotransporter 2 inhibitors (SGLT-2i). We included monotherapies and combination therapies into one regimen group in this subgroup analysis. We also summarized reported end-points and AEs by study design. The difference in characteristics between regimens was tested using Fisher's exact test. Results were considered to be statistically significant when the P-value was <0.05.

RESULTS

Study selection and regimens

The results of the literature searches are shown in Figure 1. The primary screening was carried out on 2,656 publications, and 2,511 publications were excluded: 668 were not the study design of interest; 683 did not study adult subjects with suboptimally controlled type 2 diabetes; 103 did not study any interventions of interest; 1,055 did not include Japanese subjects; and two were unable to read data from figures. Therefore, 145 of publications met the eligibility criteria shown in Table 1 after the secondary screening. All the eligible publications are listed in Table S3. Of the 145 articles, 94 were in English and 51 were in Japanese. A total of 82 were RCTs and 64 were non-RCTs. One paper included results from both an RCT and a non-RCT. A total of 284 T arms receiving any studied regimen were eligible to be summarized and analyzed; 175 (62.1%) of these arms were studied in RCTs and 107 (37.9%) in non-RCTs. In both RCTs and non-RCTs, several articles included more than two arms.

The number of eligible arms receiving each studied regimen is summarized in Table 2. In both RCTs and non-RCTs, the most studied regimen was DPP-4i, followed by insulins (basal insulin, premixed insulin and rapid-acting insulin) then GLP-1RA.

Changes in the number of arms receiving each studied regimen over the past 10 years are described in Tables S4 (RCTs) and S5 (non-RCTs), of which the percentage of arms with DPP-4i, GLP-1RA, SGLT-2i and insulin, including their combination therapies, are shown in Figure 2a,b, respectively. Regimens with DPP-4i were frequently reported in both RCTs and non-RCTs throughout the 10-year period.

In non-RCTs, SGLT2-i and GLP-1RA were also frequently studied in recent years. The number of arms studied with GLP-1RA increased after 2017. There was a trend of the insulin arm increasing in RCTs and the insulin arm decreasing in non-RCTs since 2010–2012.

Baseline characteristics

All the extracted information is shown in Table S6. In RCTs, the total percentage of arms with older adults (mean ages of ≥65 years) was 13.1%, and there was no statistical difference

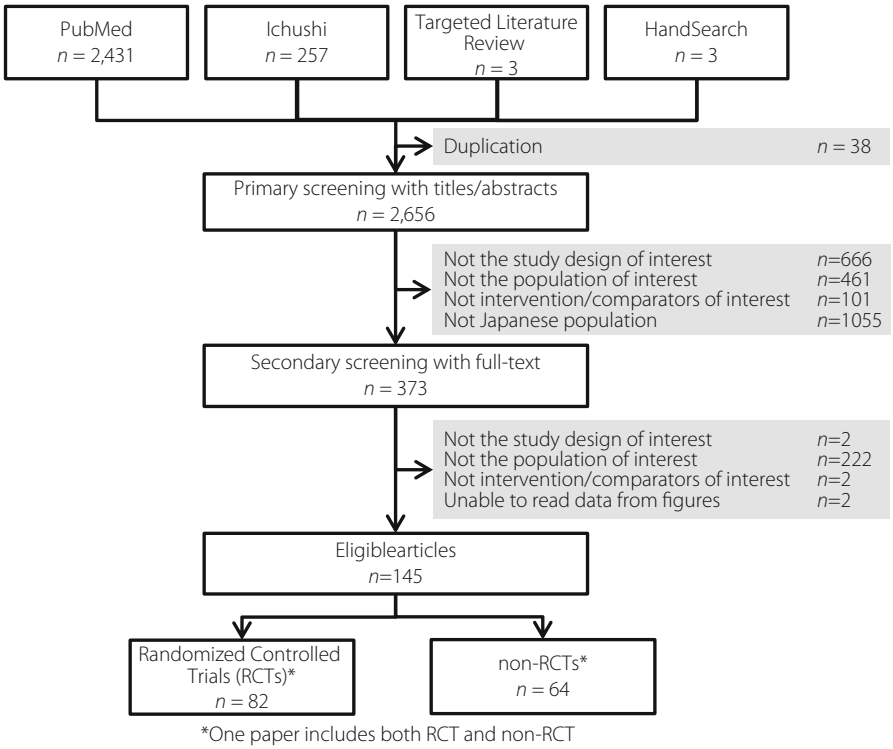

Figure 1 | Flow chart showing literature search results, screening of studies against the eligibility criteria and the final number of included studies. RCT, randomized controlled trial.

among regimen in RCTs (Figure 3a; $P = 0.052$, excluding not reported studies). The percentage of arms with obesity with the mean baseline BMI of ≥25 (the criterion for obesity[18]) was 65.1% (Figure 3b). The prevalence of obesity was statistically different among regimens, and that for SGLT-2i and GLP-1RA were higher than other arms: 83.3% and 84.0% (Figure 3b; $P = 0.014$, excluding not reported studies). This is also seen from the fact that SGLT-2i and GLP-1RA arms included more subjects with obesity than insulin arms and DPP-4i arms (Table 3). For baseline disease duration, the percentages of arms with mean type 2 diabetes disease duration of ≥10 years were statistically different among regimens as well; that is, approximately 70% in insulin, whereas it was <40% in other regimens (Figure 3c; $P < 0.001$, excluding not reported studies).

In non-RCTs, the percentage of arms with older adults was 24.3%, and included arms with mean ages of ≥75 (Figure 4a). The percentages of arms with older adults were statistically different among regimens (Figure 4a; $P < 0.001$, excluding not reported studies). The GLP-1RA and SGLT-2i arms did not include subjects aged ≥65 years, but >50% and 30% of DPP-4i and insulin arms, respectively, included the elderly, reflecting the real-world clinical practice in Japan. The percentage of arms with obesity was 44.9% (Figure 4b), and, similar to RCTs and as shown in Table 3, the percentages also showed the statistical difference among regimens, and higher for SGLT-2i and GLP-1RA: 100.0% and 68.4% (Figure 4b; $P < 0.001$, excluding not reported studies). There were no arms with mean disease duration of ≤5 years (Figure 4c). Similarly, the percentages of arms with mean disease duration of ≥10 years were statistically different and higher in insulin and DPP-4 arms (Figure 4c; $P < 0.001$, excluding not reported studies). More than 50% and 70% of DPP-4i and insulin arms, respectively, had a disease duration of ≥10 years.

In both RCTs and non-RCTs, we found that only a few arms did not report blood pressure and lipid parameters, except for SGLT-2i. In most arms, mean baseline systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides were within normal ranges based on the Japanese guidelines for dyslipidemia[19] and hypertension[20] (Table 3).

Reported end-points

HbA1c was reported as the efficacy end-point for almost all arms. Fasting blood glucose and bodyweight were also commonly reported. Compared with fasting blood glucose (58.1–94.1% in RCT, 22.7–80% in non-RCT), post-prandial blood glucose (0–66.7% in RCT, 0–21.9% in non-RCTs) was not frequently reported. Consistent with at the baseline, there were few reports on blood pressure and lipid parameters as outcomes (Table 4).

Table 2 | The number of included arms of each studied regimen in randomized controlled trials and non- randomized controlled trials

Regimen	RCT	Non-RCT
Insulin therapies	26	23
Basal insulin	20	13
Premixed insulin	6	6
Rapid-acting insulin	0	4
GLP-1 RA therapies	25	19
GLP-1 RA	23	19
GLP-1 RA + long-acting insulin	2	0
DPP-4i therapies	76	31
DPP-4i	68	28
DPP-4i + sulfonylurea	5	2
DPP-4i + biguanide	1	0
DPP-4i + glinide	0	1
DPP-4i + long-acting insulin	1	0
Sulfonylurea	3	2
Biguanide	6	1
α-Glucosidase inhibitors	2	2
α-Glucosidase inhibitors + glinide	0	4
Thiazolidine	3	4
Glinide	15	4
SGLT2i	12	17
OGLD	6	0
GPR119 agonist	2	0
Total	175	107

DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; GPR, G-protein coupled receptor; non-RCT, non-randomized controlled trial; OGLD, oral glucose-lowering drug; RCT, randomized controlled trial; SGLT-2i, sodium–glucose cotransporter 2 inhibitors.

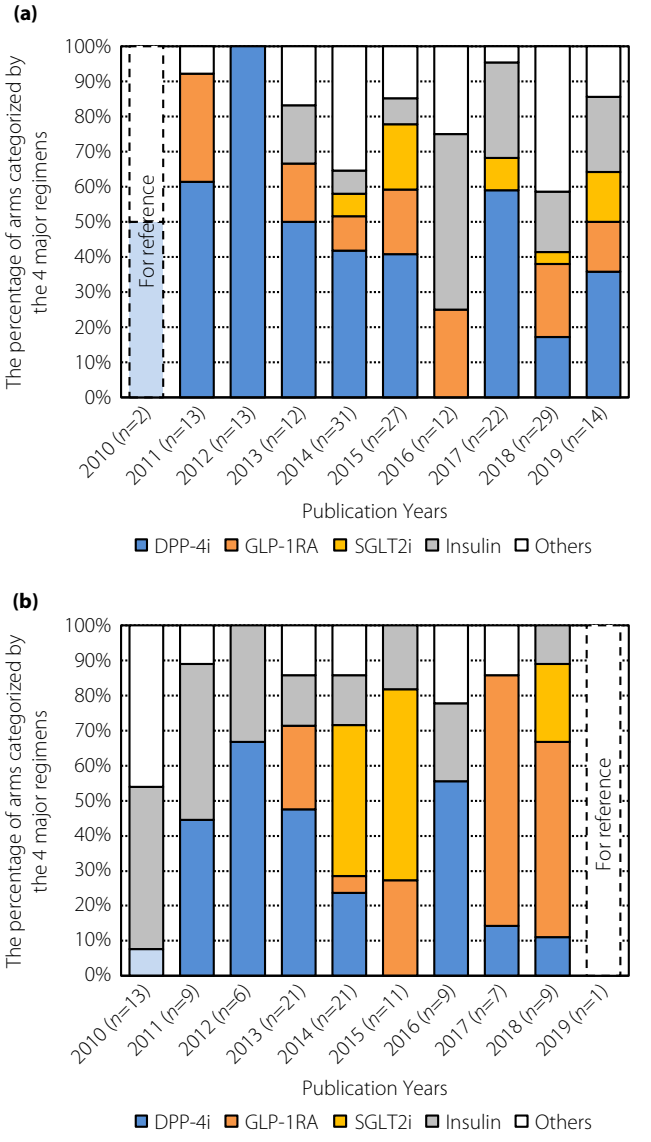

Figure 2 | Changes over the past 10 years in the percentage of arms with the four major regimens (including their combination therapies) in (a) randomized controlled trial (RCTs) and (b) non-RCTs. DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT-2i, sodium–glucose cotransporter 2 inhibitors.

Regarding safety end-points, the proportion of arms reporting safety end-points was reported in 152 of the 282 arms (53.9%). It was reported in 62.9% of the arms in RCTs, and 39.3% of the arms in non-RCTs. In RCTs, the percentage of arms reporting numbers of subjects with any AEs was approximately 60% for almost all treatments (62.7–64.0% except SGLT-2i and insulin), but it was 100.0% for SGLT-2i and 30.8% for insulin. In non-RCTs, the numbers of subjects with any AEs were more frequently reported in SGLT-2i and GLP-1RA arms than in other arms (94.1%, 94.7% and 14.1%, respectively).

DISCUSSION

The present systematic review examined RCTs and non-RCTs published in the past 10 years on Japanese individuals with type 2 diabetes. We found that DPP-4i was most commonly studied in both RCTs and non-RCTs, followed by insulins, GLP-1RA and SGLT-2i in that order. In terms of insulin, the majority was basal insulin, followed by premixed insulin. The number of arms with insulin tended to increase in RCTs and decrease in non-RCTs from 2010 to 2012. Given that the RCTs did not include the elderly with mean ages of >75 years, this might suggest the need for further research on real-world evidence of insulin in the elderly in Japan. In contrast, the number of arms with GLP-1RA increased in non-RCTs since 2017, suggesting growing interest in real-world evidence for this drug class. The total number of arms increased not only in RCTs, but also non-RCTs, after introduction of SGLT-2i to the Japanese market in 2014. The increase in the number of SGLT-2i arms might be explained by the wide variety of its compounds.

RCTs and non-RCTs showed each attribute in baseline characteristics. In RCTs, the percentage of arms with a mean age at

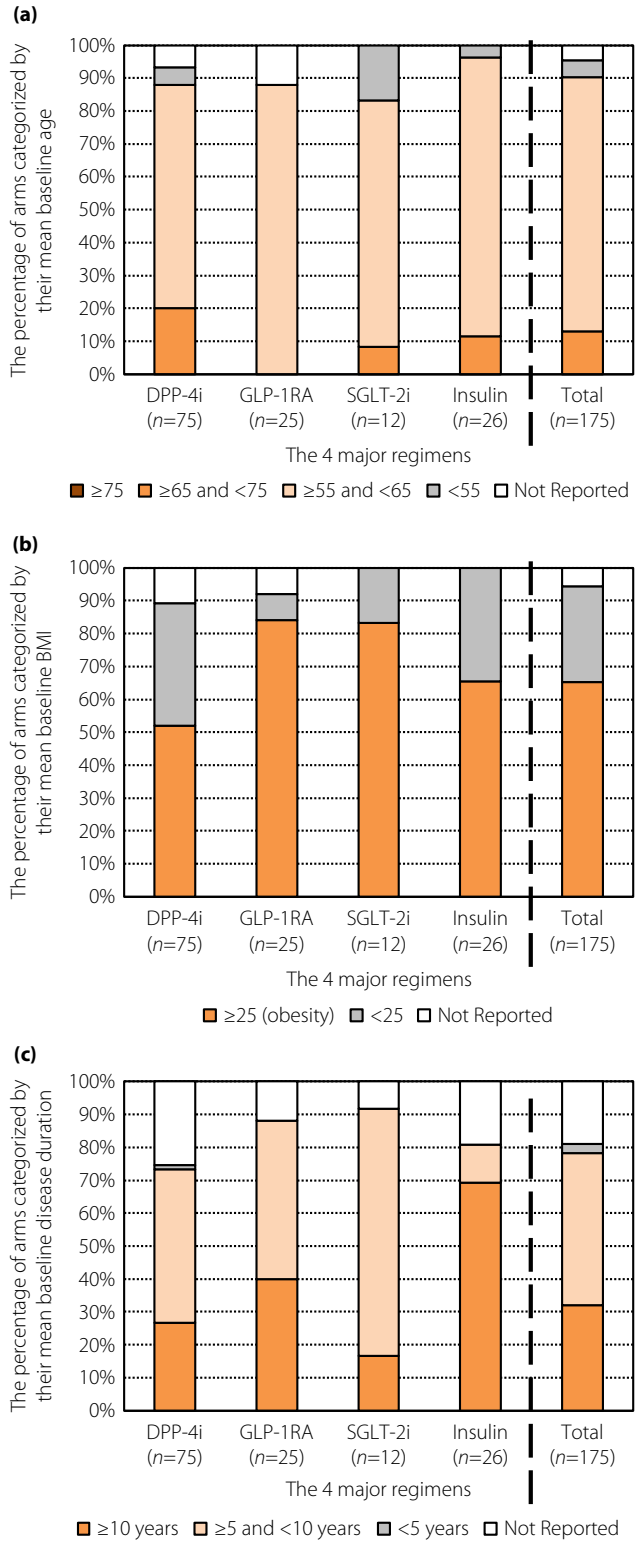

Figure 3 | The percentage of arms in randomized controlled trial (RCTs) (a) with older adults (mean baseline age of ≥65 years) for the four major regimens (including their combination therapies); (b) with obesity (mean baseline body mass index [BMI] of ≥25) for the four major regimens; and (c) with mean baseline disease duration of ≥10 years for the four major regimens. DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT-2i, sodium–glucose cotransporter 2 inhibitors.

baseline of ≥65 years was only approximately 10%, and extremely younger than the Japanese population with type 2 diabetes, whose mean age was 66.89 years in 2019, an increase of 2.68 years from 2010[4]. In RCTs, researchers are likely to refrain from enrolling older adults with consideration for aims of clinical trials or safety reasons: individuals aged ≥75 years were not enrolled, and those aged ≥65 years were also rare. In contrast, non-RCTs are considered to reflect the clinical practice. Such aspects of RCTs need to be taken into consideration when the study results are applied to the clinical practice, and more post-marketing studies including subjects aged ≥65 years would be beneficial.

In non-RCT arms, the baseline demographic characteristics and BMI seemed to have been reflecting the real-world practice. For example, SGLT-2i arms and GLP-1RA arms showed that higher percentage of arms with obesity (mean BMI of ≥25), and lower percentage of arms with older adults (mean age of ≥65 years) than arms with other regimens, as they are recommended to relatively young and obese type 2 diabetes patients[21]. Similarly, the higher percentage of arms with older adults in DPP-4i arms suggests clinicians' prescription choices in regard to some safety concerns. For insulin arms, the percentage of arms with mean disease duration of ≥10 years was high, reflecting subject with type 2 diabetes who have not been adequately controlled with oral antidiabetic drugs.

In contrast, in RCTs, differences of baseline characteristics among regimens were small. This might result from enrolling subjects sampled from the overall type 2 diabetes population based on strict protocols. The proportions of adults aged ≥65 years and having obesity with BMI of ≥25 in the present study were 13.1% and 65.1%, respectively, which was extremely younger and slightly obese compared with the Japanese population with type 2 diabetes registered in the Japan Diabetes Clinical Data Management Study Group[22,23]. During the decade from 2010 to 2019, the means of age and BMI changed from 64.21 to 66.89 years and from 24.69 to 24.81, respectively[5]. Notably, in RCTs, only approximately 20% of the DPP-4i arms targeted the elderly or individuals with type 2 diabetes disease duration of ≥10 years, whereas in non-RCTs, the proportion was >50%, suggesting that the RCTs do not reflect the reality of treatment status, and that DPP-4is are used for a longer term in the elderly as relatively safe drugs in the actual clinical practice[21].

In almost all arms in both RCTs and non-RCTs, the reported mean blood pressure and lipid parameters at baseline were within the normal range by the criteria of Japanese guidelines[19,20]. This suggests that the studied drugs are intended for individuals without hypertension or dyslipidemia. Blood

Table 3 | Baseline characteristics of included arms for the four major regimens (including their combination therapies)

	RCT (n = 175)								Non-RCT (n = 107)							
	Insulin		DPP-4i		SGLT-2i		GLP1-RA		Insulin		DPP-4i		SGLT-2i		GLP1-RA	
Total	26		75		12		25		23		31		17		19	
Age (years)																
<55	1	3.8%	4	5.3%	2	16.7%	0	0.0%	1	4.3%	0	0.0%	3	17.6%	1	5.3%
≥55 & <65	22	84.6%	51	68.0%	9	75.0%	22	88.0%	12	52.2%	13	41.9%	14	82.4%	16	84.2%
≥65 & <75	3	11.5%	15	20.0%	1	8.3%	0	0.0%	5	21.7%	15	48.4%	0	0.0%	0	0.0%
≥75	0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	8.7%	1	3.2%	0	0.0%	0	0.0%
Not reported	0	0.0%	5	6.7%	0	0.0%	3	12.0%	3	13.0%	2	6.5%	0	0.0%	2	10.5%
Duration (years)																
<5	0	0.0%	1	1.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
≥5 & <10	3	11.5%	35	46.7%	9	75.0%	12	48.0%	3	13.0%	2	6.5%	16	94.1%	9	47.4%
≥10	18	69.2%	20	26.7%	2	16.7%	10	40.0%	16	69.6%	18	58.1%	0	0.0%	3	15.8%
Not reported	5	19.2%	19	25.3%	1	8.3%	3	12.0%	4	17.4%	11	35.5%	1	5.9%	7	36.8%
BMI																
<25[†]	9	34.6%	28	37.3%	2	16.7%	2	8.0%	14	60.9%	18	58.1%	0	0.0%	4	21.1%
≥25[†]	17	65.4%	39	52.0%	10	83.3%	21	84.0%	5	21.7%	9	29.0%	17	100.0%	13	68.4%
Not reported	0	0.0%	8	10.7%	0	0.0%	2	8.0%	4	17.4%	4	12.9%	0	0.0%	2	10.5%
LDL-C (mg/dL)																
<140[‡]	6	23.1%	26	34.7%	11	91.7%	8	32.0%	6	26.1%	15	48.4%	16	94.1%	3	15.8%
≥140[‡]	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Not reported	20	76.9%	49	65.3%	1	8.3%	17	68.0%	17	73.9%	16	51.6%	1	5.9%	16	84.2%
HDL-C (mg/dL)																
<40[‡]	0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	8.7%	0	0.0%	0	0.0%	0	0.0%
≥40[‡]	6	23.1%	26	34.7%	11	91.7%	9	36.0%	5	21.7%	16	51.6%	16	94.1%	3	15.8%
Not reported	20	76.9%	49	65.3%	1	8.3%	16	64.0%	16	69.6%	15	48.4%	1	5.9%	16	84.2%
TG (mg/dL)																
<150[‡]	6	23.1%	18	24.0%	6	50.0%	7	28.0%	7	30.4%	8	25.8%	12	70.6%	0	0.0%
≥150[‡]	0	0.0%	7	9.3%	2	16.7%	2	8.0%	1	4.3%	2	6.5%	4	23.5%	4	21.1%
Not reported	20	76.9%	50	66.7%	4	33.3%	16	64.0%	15	65.2%	21	67.7%	1	5.9%	15	78.9%
SBP (mmHg)																
<140[§]	3	11.5%	21	28.0%	10	83.3%	3	12.0%	4	17.4%	17	54.8%	16	94.1%	1	5.3%
≥140[§]	0	0.0%	1	1.3%	1	8.3%	0	0.0%	2	8.7%	0	0.0%	0	0.0%	0	0.0%
Not reported	23	88.5%	53	70.7%	1	8.3%	22	88.0%	17	73.9%	14	45.2%	1	5.9%	18	94.7%
DBP (mmHg)																
<90[§]	1	3.8%	21	28.0%	11	91.7%	2	8.0%	6	26.1%	17	54.8%	16	94.1%	1	5.3%
≥90[§]	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Not reported	25	96.2%	54	72.0%	1	8.3%	23	92.0%	17	73.9%	14	45.2%	1	5.9%	18	94.7%

[†]Criteria of obesity in Ref. [18]. [‡]Criteria of dyslipidemia in Ref. [19]. [§]Criteria of hypertension in Ref. [20]. BMI, body mass index; DBP, diastolic blood pressure; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; non-RCT, non-randomized controlled trial; RCT, randomized controlled trial, SBP, systolic blood pressure; SGLT-2i, sodium glucose cotransporter-2 inhibitors; TG, triglyceride.

pressure and lipid parameters at baseline were rarely reported, except for SGLT-2, also known for improving blood pressure and lipids; therefore, the presence or absence of hypertension or dyslipidemia could not be detected. Individuals with a longer duration of type 2 diabetes, especially those using insulins, might have an increased risk of cardiovascular diseases. Therefore, it is also important to include blood pressure and lipid levels.

As efficacy end-points, most studies reported HbA1c, fasting blood glucose and bodyweight. In contrast, blood pressure or lipid parameters were not reported frequently. This is consistent with the data that blood pressure and lipid parameters were rarely reported, even at baseline, in the GLP-1RA and insulin arms. It is important to know the status of complications in individuals with long-term disease duration who use insulin and other drugs. Thus, this might be one of the data gaps awaiting further study.

We found that the percentage of arms reporting the number of subjects with any AEs was approximately 40% in non-RCTs and >60% in RCTs. This might be because RCTs are designed to collect and report safety information. The number of subjects with any AEs was reported in almost all SGLT-2i arms in

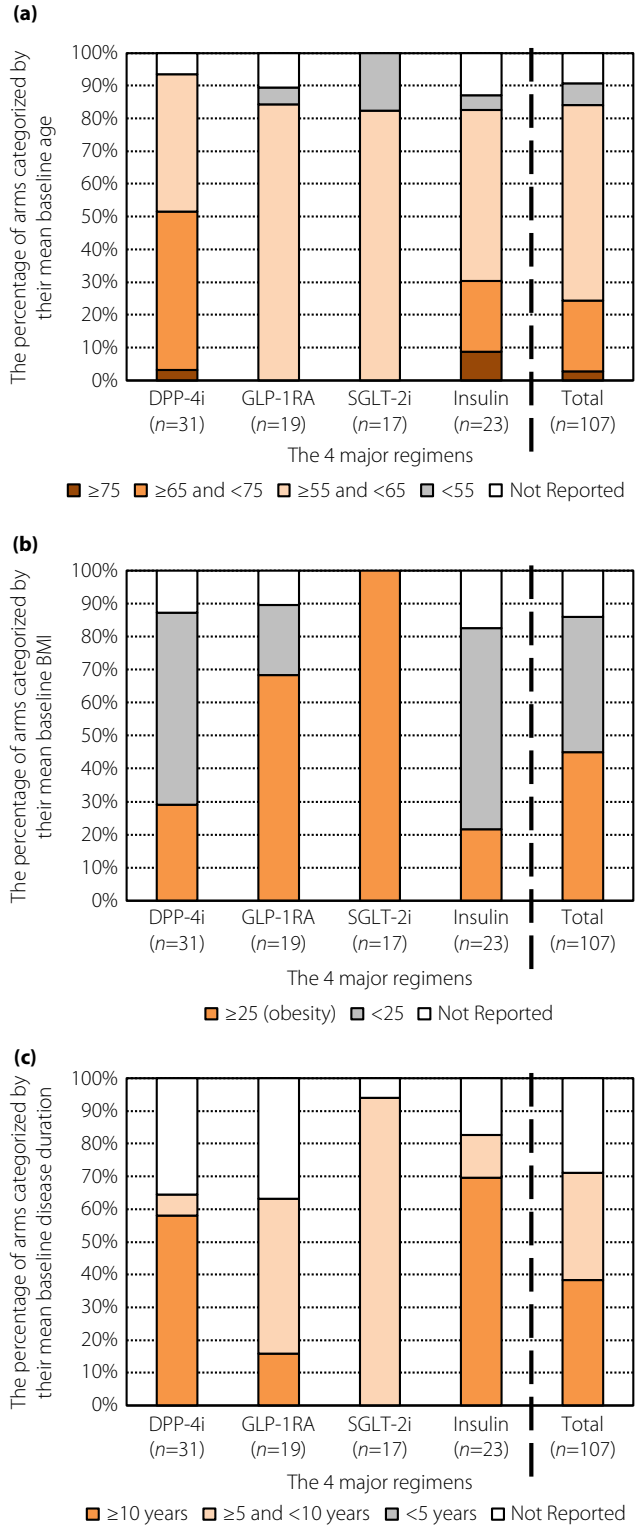

Figure 4 | The percentage of arms in non-randomized controlled trials (RCTs) (a) with older adults (mean baseline age of ≥65 years) for the four major regimens (including their combination therapies); (b) with obesity (mean baseline body mass index [BM]l of ≥25) for the four major regimens; and (c) with mean baseline disease duration of ≥10 years for the four major regimens. DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT-2i, sodium–glucose cotransporter-2 inhibitors.

both RCTs and non-RCTs; this might suggest the greater clinical interest in AEs for this drug. We examined whether the incidence of AEs was reported or not, but did not examine whether mild hypoglycemia was included in the reported AEs or not; thus, the study status regarding hypoglycemia in regimens for type 2 diabetes is unclear.

Eligible publications were written in both English and Japanese (Table S3). The proportion of Japanese publications was higher for non-RCTs (57.8%, 37/64) than for RCTs (17.3%, 14/81). In both study designs, on the whole, fewer DPP-4is were reported in articles excluding those written in Japanese than articles including those written in Japanese (see Figure S1 after excluding Japanese articles from Figure 2). It was suggested that articles published particularly for information sharing and decision-making in the daily clinical practice are written in Japanese.

We found that the percentage of elderly, obese subjects and longer disease duration varied according to the studied drugs in both RCTs and non-RCTs, and in non-RCTs, it would also reflect the characteristics of individuals who were likely to be prescribed those drugs. In both RCTs and non-RCTs, the results were essentially similar between articles excluding those written in Japanese and those including those written in Japanese with respect to age, obesity or disease duration, as shown in Figures S2 (RCTs) and S3 (non-RCTs) (excluding Japanese) compared with Figures 3 (RCTs) and 4 (non-RCTs; including Japanese), respectively. The research community cannot simply assume that the results of a study fully represent real-world clinical practice, just because the study results were obtained from RCT or non-RCT, as also confirmed from the other study[24]. To correctly interpret the generalizability of study results, researchers need to closely examine the study designs and backgrounds.

Although recent studies have increasingly focused on real-world data from claims databases, we could not include them in non-RCTs as a result, because the efficacy end-points, such as bodyweight and the results of blood examinations, can be rarely obtained from the claims databases. Second, we did not evaluate the risk of bias, because we extracted and abstracted information from studies with various study designs; thus, the present findings might have been affected by any bias in the included studies. However, we believe that the effect of bias on our discussion and conclusion is limited, because we only summarized and described the reported information on the background and end-points of studies, and did not integrate or compare outcome values. Finally, we did not analyze quality of life or adherence, because these data were not reported for enough arms.

Table 4 | Changes in percentage of arms reporting each efficacy end-point

Study design	Publication year	#	HbA1c (%)	Fasting blood glucose (%)	Post-prandial blood glucose (%)	Lipid (%)†	Blood pressure (%)‡	Bodyweight (%)
RCT (n = 175)	2010–2011	15	14 (93.3)	12 (80.0)	10 (66.7)	8 (53.3)	1 (6.7)	13 (86.7)
	2012–2013	25	25 (100.0)	17 (68.0)	8 (32.0)	16 (64.0)	2 (8.0)	12 (48.0)
	2014–2015	58	55 (94.8)	43 (74.1)	16 (27.6)	20 (34.5)	13 (22.4)	43 (74.1)
	2016–2017	34	32 (94.1)	32 (94.1)	0 (0.0)	4 (11.8)	4 (11.8)	25 (73.5)
	2018–2019	43	36 (83.7)	25 (58.1)	15 (34.9)	16 (37.2)	12 (27.9)	28 (65.1)
Non-RCT (n = 107)	2010–2011	22	22 (100.0)	5 (22.7)	4 (18.2)	2 (9.1)	1 (4.5)	7 (31.8)
	2012–2013	27	21 (77.8)	10 (37.0)	3 (11.1)	11 (40.7)	6 (22.2)	14 (51.9)
	2014–2015	32	26 (81.3)	22 (68.8)	7 (21.9)	22 (68.8)	20 (62.5)	21 (65.6)
	2016–2017	16	12 (75.0)	11 (68.8)	2 (12.5)	5 (31.3)	3 (18.8)	6 (37.5)
	2018–2019	10	10 (100.0)	8 (80.0)	0 (0.0)	4 (40.0)	1 (10.0)	10 (100.0)

†Any of triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. ‡Any of systolic blood pressure and diastolic blood pressure. Non-RCT, non-randomized controlled trial; RCT, randomized controlled trial.

In conclusion, in the present systematic review, we comprehensively examined the studied regimens in the past 10 years in RCTs and non-RCTs on Japanese adults with suboptimally controlled type 2 diabetes despite receiving glucose-lowering drugs. We focused on studied regimens, baseline characteristics and reported end-points.

DPP-4i was most frequently studied in both RCTs and non-RCTs. The majority of subjects in RCTs had common type 2 diabetes, as defined by the inclusion criteria, whereas subjects in non-RCTs reflected actual clinical practice; that is, more individuals who are aged ≥65 years and have longer type 2 diabetes disease duration. Therefore, to better understand the unmet needs of type 2 diabetes treatment, it is essential to assess the baseline characteristics and reported end-points carefully, from the perspectives of real-word clinical practice in Japan and the generalizability of each study. Furthermore, it was suggested that the clinical guidelines should be interpreted properly, with findings from both RCTs and non-RCTs complementarily.

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DISCLOSURE

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Approval of the research protocol: The protocol was prepared in accordance with the PRISMA statement[16] and PRISMA-P statement[17]. It was registered at the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42020170888).
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Changes over the past 10 years in the percentage of arms with the 4 major regimens (including their combination therapies) in (a) randomized controlled trials and (b) non-randomized controlled trials excluding Japanese articles.

Figure S2 | The percentage of arms in randomized controlled trials excluding Japanese articles: (a) with older adults (mean baseline age of 65 or older) for the four major regimens (including their combination therapies); (b) with obesity (mean baseline body mass

index of ≥25) for the four major regimens; (c) with mean baseline disease duration of 10 years or longer for the four major regimens.

Figure S3 | The percentage of arms in non-randomized controlled trials excluding Japanese articles: (a) with older adults (mean baseline age of ≥65 years) for the four major regimens (including their combination therapies); (b) with obesity (mean baseline BMI of ≥25) for the four major regimens; (c) with mean baseline disease duration of ≥10 years for the four major regimens.

Table S1 | The PubMed search strategy.

Table S2 | The ICHUSHI search strategy.

Table S3 | List of eligible studies.

Table S4 | Changes over the past 10 years in the number of arms with each studied regimen in randomized controlled trials.

Table S5 | Changes over the past 10 years in the number of arms with each studied regimen in non-randomized controlled trials.

Table S6 | Extracted baseline conditions for arms.