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ORIGINAL ARTICLE

Use of diabetes medications in adults with T2D and CVD in Japan: secondary analysis of the CAPTURE study

Yukiko Onishi[1] · Shinichiro Shirabe[2] · Kosei Eguchi[3] · Keiji Nishijima[3] · Toshihiro Sato[3] · Hiroaki Seino[4]

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Abstract

Introduction The CAPTURE study estimated the global prevalence of established cardiovascular disease (CVD) and characterized the usage of glucose-lowering agents (GLAs) in adults with type 2 diabetes (T2D) across 13 countries. The purpose of this secondary analysis of data from the Japanese sites within CAPTURE (NCT03786406, NCT03811288) was to provide data about medication usage stratified by CVD status among Japanese participants with T2D.

Materials and methods Data on GLA usage (including those with proven cardiovascular [CV] benefits) in Japanese participants with T2D managed in clinics or hospitals were collected and stratified by CVD subgroups.

Results There were 800 Japanese participants in the CAPTURE study ($n=502$ [no CVD group], $n=298$ [CVD group], $n=268$ [atherosclerotic CVD subgroup]). Oral antidiabetic agents and insulin were used by 88.5% and 23.4%, respectively, of participants overall. Among participants with established CVD, dipeptidyl peptidase-4 inhibitors (65.1%) were most frequently used, followed by biguanides (50.7%) and insulins (26.2%). The pattern was similar among participants with atherosclerotic CVD. A lower proportion of participants in the CVD group used glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT-2is) with proven CV benefits versus the no CVD group (GLP-1 RAs: 7.0% vs. 8.6%; SGLT-2is: 13.4% vs. 19.1%).

Conclusion This analysis of the CAPTURE study provided a comprehensive overview of prescription patterns for the treatment of T2D in Japan. Use of GLAs with proven CV benefit was low, even in participants with established CVD, which was comparable to the findings from the global cohort.

Keywords Diabetes mellitus, type 2 · Glucagon-like peptide-1 · Sodium-glucose cotransporter-2 inhibitors

Introduction

The prevalence of diabetes (types 1 [T1D] and 2 [T2D]) in Japanese adults was 7.9% in 2019 according to the International Diabetes Federation [1]. A meta-analysis of 102 prospective studies reported that, independent of other conventional risk factors, patients with diabetes had a two-fold greater risk of numerous vascular diseases such as coronary heart disease (CHD) than those without diabetes [2]. Specifically, for example, according to the Japan Diabetes Complications Study, the crude incidence of myocardial infarction (MI) in patients with diabetes (3.84 per 1000 patient-years) was greater than in the general population (0.65–1.42 per 1000 patient-years) [3]. Diabetes is therefore considered among the top four healthcare priorities by the Japanese government [4]. However, a survey by the Japan National Health and Nutrition Surveys (2003–2012) in 51,128 Japanese adults reported that diabetes management was inadequate for preventing vascular complications [4].

The glucose-lowering agents (GLAs) commonly used in Japan include sulfonylureas (SUs), glinides, dipeptidyl peptidase-4 inhibitors (DPP-4is), biguanides, thiazolidinediones (TZDs), alpha-glucosidase inhibitors, sodium-glucose cotransporter-2 inhibitors (SGLT-2is), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and insulins. Several cardiovascular outcome trials (CVOTs) have shown

✉ Yukiko Onishi
y-ohnishi@asahi-life.or.jp

1 The Institute of Medical Science, Asahi Life Foundation, 2-2-6 Nihonbashibakurocho, Chuo-ku, Tokyo 103-0002, Japan

2 HEC Science Clinic, Yokohama, Japan

3 Novo Nordisk Pharma Ltd., Tokyo, Japan

4 Seino Internal Medicine Clinic, Fukushima, Japan

cardiovascular (CV) risk reduction with some GLP-1 RAs or SGLT-2is versus placebo [5–10], and this reduction may impact upon Asians more than Caucasians [11]. Unlike guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [12, 13], the Japanese Clinical Practice Guideline for Diabetes 2019 does not specifically recommend agents with CV benefits [14], but a consensus statement from the Japanese Circulation Society (JCS) and the Japan Diabetes Society (JDS) includes such a recommendation [15].

The usage of GLAs in Japan appears to be different from other countries. While a few studies have investigated the use of GLAs within Japan [16], very few compare medication use simultaneously across several countries including Japan. Recently, the CAPTURE study, which was conducted across 13 countries simultaneously, estimated the global prevalence of established cardiovascular disease (CVD) in adults with T2D and compared GLAs and CVD medication use in participants with and without CVD [17]. The CAPTURE study also evaluated the usage of GLAs and CV medications in these participants with specific reference to GLAs demonstrating CV benefit [17].

The present analysis builds upon the CAPTURE Japan data previously published [18], which aimed to measure the prevalence and pattern of CVD among adults with T2D across 20 centers in Japan that took part in the CAPTURE study. The purpose of this secondary analysis was to provide data about medication usage stratified by CVD status among Japanese participants with T2D.

Materials and methods

Study design

The CAPTURE study was a cross-sectional, non-interventional study conducted at 214 centers in 13 countries between December 2018 and September 2019. Of these, 20 participating centers were from Japan. The full methods of the CAPTURE study (NCT03786406 and NCT03811288) have been previously published [17]. Adults (≥ 20 years) with diagnosis of T2D ≥ 180 days prior to providing informed consent were included, whereas adults with T1D or known congenital heart disease or malformation were excluded [17]. Available demographic, anthropometric, and clinical parameters were collected during a single visit [17, 18].

Diabetologists and general practitioners managing T2D in daily medical practice participated in the study. The clinical management of T2D and the treatments prescribed were entirely at the discretion of these physicians. In the current analysis, data specific to participants from Japan were analyzed.

Data recorded

Data on GLAs (current medications or those discontinued within the previous 3 months) used were the focus of this analysis; these medications included: biguanides, TZDs, SUs, glinides, DPP-4is, alpha-glucosidase inhibitors, SGLT-2is, GLP-1 RAs, and insulins. Participants were categorized based on CVD status: no CVD (patients without CVD), CVD (patients with CVD), and those with atherosclerotic cardiovascular disease (ASCVD; a subset of CVD). During this analysis, GLP-1 RAs and SGLT-2is were further categorized according to demonstrated CV benefit status, in line with the 2022 ADA guidelines [19, 20]. The GLAs with demonstrated CV benefit were three subcutaneous GLP-1 RAs (once-weekly dulaglutide, once-daily liraglutide, and once-weekly semaglutide) and three oral once-daily SGLT-2is (canagliflozin, dapagliflozin, and empagliflozin). The CVD medications used by participants were also analyzed.

Definitions of CV variables used

Established CVD was defined as any of the following conditions listed as a diagnosis in a participant's medical records: cerebrovascular disease, CHD, heart failure (HF), cardiac arrhythmia or conduction abnormalities, aortic diseases, peripheral arterial disease (PAD), or carotid artery disease [17]. ASCVD (a subgroup of CVD and an important cause of morbidity and mortality in patients with T2D [20]) was similarly defined as a diagnosis of cerebrovascular disease, CHD, PAD, or carotid artery disease [17].

Ethics

The CAPTURE study was conducted in accordance with the Declaration of Helsinki [21], International Society for Pharmacoepidemiology Good Pharmacoepidemiology Practices [22], and local regulations for clinical research in Japan. The study protocol was approved by the clinical research ethics committee and institutional review board at each site, and written informed consent was provided by all participants [17, 18].

Statistical analysis

Full details of the statistical methodology for CAPTURE have been published previously [17]. Demographic and clinical characteristics of the CAPTURE study sample in Japan were analyzed according to CVD status. Data were analyzed descriptively, with no statistical comparisons performed. Data on GLA usage were also stratified based on

CVD subgroups, number of GLAs used, age, body mass index (BMI), estimated glomerular filtration rate (eGFR), and GLAs with proven CV benefits. Data on CVD status and GLAs used by participants in clinics (outpatients) and hospitals were measured. All statistical analyses were carried out using Statistical Analysis Software (SAS), version 9.4 (SAS Institute, NC, USA).

Results

Baseline characteristics of participants according to CVD status

The CAPTURE study enrolled 9823 adults with T2D, of whom 800 were from Japan [17, 18]. Of these, 502 (62.8%) did not have CVD (no CVD group), 298 (37.3%) had CVD (CVD group), and 268 (33.5%) had ASCVD (ASCVD subgroup) [17, 18]. Demographic and clinical characteristics are summarized in Table 1.

GLA usage by CVD subgroups

Oral antidiabetic drugs (OADs) were prescribed to a similar proportion of participants (88.1–88.6%) across the three CVD groups (Fig. 1). Insulin was prescribed to 21.7%, 26.2%, and 27.2% of the participants in the no CVD, CVD, and ASCVD subgroups, respectively (Fig. 1). Among participants with CVD, DPP-4is (65.1%) were most frequently used, followed by biguanides (50.7%), insulins (26.2%), and SGLT-2is (25.8%). Among those with ASCVD, the pattern was similar: DPP-4is (64.6%) were most frequently used, followed by biguanides (51.1%), insulins (27.2%), and SGLT-2is (25.7%). Most of the participants in the no CVD group (30.3%), CVD group (35.2%), and ASCVD subgroup (35.1%) received dual therapy (Fig. S1). Table S1 provides details on medication use in clinics and hospitals.

GLA usage stratified by age, BMI, and eGFR

Most of the participants aged 20–45 years received biguanides (76.9%), followed by SGLT-2is (59.0%) and DPP-4is (48.7%). The majority of participants aged ≥ 75 years received DPP-4is (71.0%), followed by biguanides (41.5%) and insulins (26.7%) (Fig. S2). Diabetes medication usage stratified by both age and CVD status is presented in Fig. S3. Insulin use varied more with age in those with CVD versus those without CVD (Fig. S3).

The majority of participants with normal BMI (18.5–24.9 kg/m^2) and with BMI 25–≤ 29.9 kg/m^2 received DPP-4is (64.4% and 59.5%, respectively) (Fig. S4). Participants with BMI 30–≤ 34.9 kg/m^2 mostly received biguanides (59.4%), followed by DPP-4is (52.2%) and SGLT-2is (39.1%). Participants with BMI ≥ 35.0 kg/m^2 mostly received biguanides (70.0%), followed by SGLT-2is (60.0%), DPP-4is (40.0%), and GLP-1 RAs (35.0%).

Most of the participants with eGFR > 89 mL/min/1.72 m^2 and > 59–≤ 89 mL/min/1.72 m^2 received biguanides (70.3%)

Table 1 Demographic and clinical characteristics of the CAPTURE study sample in Japan stratified by CVD status

Characteristic[a]	Overall (n = 800)	By CVD status		
		No CVD (n = 502)	CVD (n = 298)	ASCVD[b] (n = 268)
Male, n (%)	537 (67.1)	334 (66.5)	203 (68.1)	185 (69.0)
Female, n (%)	263 (32.9)	168 (33.5)	95 (31.9)	83 (31.0)
Age, years	65.6 (11.2)	63.0 (11.0)	70.0 (10.1)	70.2 (9.9)
Diabetes duration, years	13.5 (9.0)	12.1 (7.9)	16.0 (10.2)	16.3 (10.3)
HbA1c, %	7.2 (0.9)	7.2 (1.0)	7.2 (0.9)	7.3 (0.9)
FPG, mg/dL	141.8 (39.5)	141.0 (38.2)	143.7 (42.6)	144.1 (41.8)
Body weight, kg	67.8 (13.8)	68.7 (14.0)	66.3 (13.2)	65.7 (12.4)
BMI, kg/m^2	25.6 (4.2)	25.8 (4.4)	25.2 (4.0)	25.0 (3.7)
Systolic blood pressure, mmHg	132.4 (14.7)	132.5 (14.6)	132.4 (14.9)	132.7 (15.0)
Diastolic blood pressure, mmHg	75.8 (10.5)	77.4 (10.1)	73.2 (10.7)	73.2 (10.7)
Total cholesterol, mg/dL	186.9 (37.0)	193.5 (35.8)	173.9 (35.9)	174.7 (36.7)
LDL cholesterol, mg/dL	104.3 (31.1)	109.8 (31.2)	94.7 (28.6)	93.9 (28.7)
HDL cholesterol, mg/dL	56.6 (15.7)	57.9 (15.9)	54.3 (15.0)	55.0 (15.2)
Triglycerides, mg/dL	149.3 (89.4)	150.0 (92.4)	148.1 (83.9)	147.2 (84.0)

Data are mean (standard deviation) unless otherwise indicated

[a]Number of observations differs for each characteristic. [b]ASCVD is a subgroup of CVD

ASCVD atherosclerotic cardiovascular disease, *BMI* body mass index, *CVD* cardiovascular disease, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

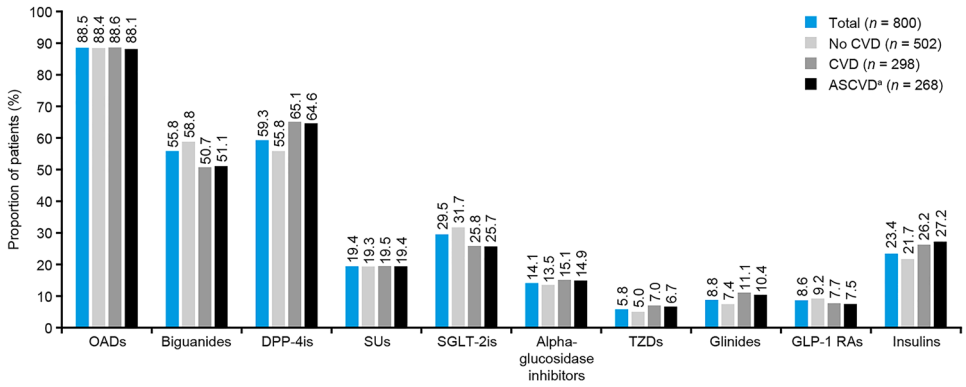

Fig. 1 Diabetes medication usage stratified by CVD groups among CAPTURE study participants in Japan. [a]ASCVD is a subgroup of CVD. *ASCVD* atherosclerotic cardiovascular disease, *CVD* cardiovascular disease, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *OAD* oral antidiabetic drug, *SGLT-2i* sodium-glucose cotransporter-2 inhibitor, *SU* sulfonylurea, *TZD* thiazolidinedione

or DPP-4is (60.8%), respectively (Fig. S5). Insulin was the most used GLA among the participants with eGFR ≤29 mL/min/1.72 m^2 (63.2%) (Fig. S5).

GLAs with proven CV benefit

Usage of SGLT-2is with proven CV benefit was lower in the CVD group versus the no CVD group (SGLT-2is: 13.4% vs. 19.1%), whereas that of GLP-1 RAs with proven CV benefit was similar (GLP-1 RAs: 7.0% vs. 8.6%) (Fig. 2). Overall, dulaglutide (4.4%) was the most frequently used GLP-1 RA, followed by liraglutide (2.4%) and semaglutide (1.3%). Empagliflozin (7.0%) was the most frequently used SGLT-2i, followed by canagliflozin (5.3%), and dapagliflozin (4.8%) (Fig. 2).

CVD medications commonly used

Overall, 42.4% of the participants were prescribed medications for hypertension and other CVDs. The proportions of participants receiving these medications were similar in the CVD and ASCVD subgroups (59.1% vs. 59.0%) (Fig. 3). After medications for hypertension and other CVDs, lipid-lowering agents were the next most frequently utilized in the no CVD (31.9%), CVD (52.7%), and ASCVD (56.0%) subgroups (Fig. 3); of these, statins were the most commonly used ($n = 282$ [35.3%]), irrespective of CVD subgroup. Details on commonly used CVD medications in clinics and hospitals are provided in Table S1.

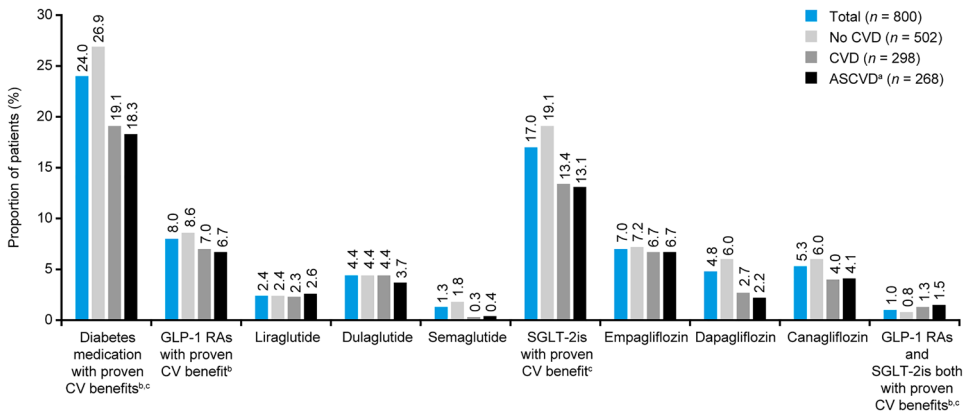

Fig. 2 Usage of diabetes medication with proven CV benefit stratified by CVD groups among CAPTURE study participants in Japan. [a]ASCVD is a subgroup of CVD. [b]Subcutaneous administration: once-weekly dulaglutide, once-daily liraglutide, once-weekly semaglutide. [c]Oral administration (all once daily): empagliflozin, canagliflozin, dapagliflozin. *ASCVD* atherosclerotic cardiovascular disease, *CVD* cardiovascular disease, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *SGLT-2i* sodium-glucose cotransporter-2 inhibitor

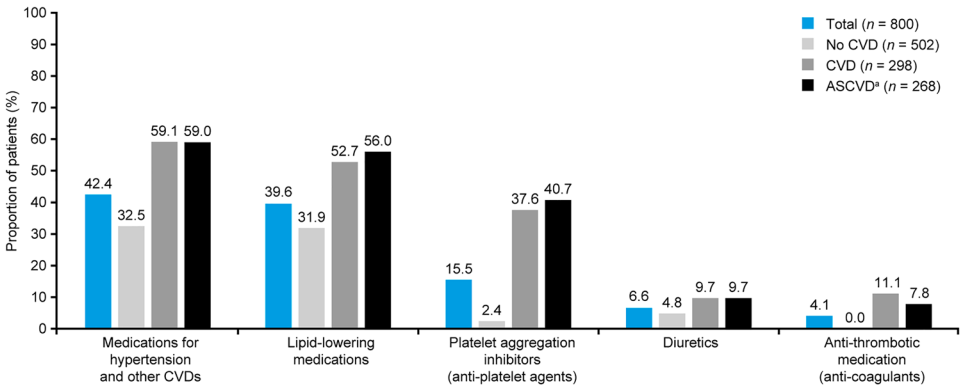

Fig. 3 CVD medication usage stratified by CVD groups among CAPTURE study participants in Japan. [a]ASCVD is a subgroup of CVD. Of the lipid-lowering medications, statins were used by 282 (35.3%) in total, irrespective of CVD group. *ASCVD* atherosclerotic cardiovascular disease, *CVD* cardiovascular disease

Discussion

This secondary analysis of the CAPTURE study examined medication usage in the total population and in subgroups according to CVD status, among participants with T2D across 20 centers in Japan. Overall, 88.5% of the Japanese participants with T2D were prescribed OADs. DPP-4is were the most commonly used OADs among Japanese participants, whereas biguanides were the most used among global participants in the CAPTURE study [17]. Compared with the global participants, the CVD group within the Japanese population used DPP-4is more frequently (65.1% vs. 27.2%) and biguanides less frequently (50.7% vs. 70.6%) [17].

Japanese patients with T2D have lower insulin secretion compared with other ethnic populations and therefore insulin secretagogues like DPP-4is are a preferred treatment option [23, 24]. The findings from our analysis agree with earlier reports on high DPP-4i usage in Japan compared with other countries [25–28]. The preference to use DPP-4is in Japan might be due to their efficacy and safety [29, 30], infrequent dosing, fewer adverse events, and weight neutrality [31, 32]. Unlike in the USA (ADA) and Europe (EASD) [33], the Japanese guideline does not recommend any specific antidiabetic agent in the first-line treatment of patients with T2D [14, 34]. It is thus not surprising that differences in prescribing patterns in T2D between Japan and other countries were evident in this study.

In comparison with the global CAPTURE participants, a lower proportion of Japanese participants used insulin (37.7% vs. 23.4%), despite having a mean diabetes duration of ≈14 years [17]. Within the CVD group, insulin usage was lower in the Japanese participants (26.2%) compared with global participants (44.8%) [17]. Other studies have cited that the lower insulin usage in the Japanese participants may be attributed to fear of hypoglycemia and non-suitability to the Japanese lifestyle [35–37]. As per the Japanese Clinical Practice Guideline for Diabetes 2019, within the clinical setting, insulin therapy is only recommended in Japanese patients who do not reach their glycemic goal with diet, exercise therapy, and OADs [14].

Apart from the lower insulin usage, utilization of GLP-1 RAs was also lower among Japanese participants versus global participants [17], and was lower compared with other diabetes medications used in Japan. This is despite the fact that real-world evidence of GLP-1 RAs in improving glycated hemoglobin (HbA1c), body weight, and lipid profiles compared with baseline has been established using the Japan Diabetes Clinical Data Management Study Group (JDDM) database [38]. Furthermore, the GLP-1 RAs liraglutide, dulaglutide, and semaglutide, and the SGLT-2is empagliflozin and canagliflozin have shown positive outcomes in Japanese patients with T2D [39–43].

According to the JCS and JDS, GLP-1 RAs and SGLT-2is may be useful in the reduction of 3-point major adverse cardiovascular events (MACE) in patients with T2D [15]. Despite this, the present analysis revealed a risk-treatment paradox in use of GLP-1 RAs; the usage of such agents with beneficial CV outcomes was somewhat lower in the CVD and ASCVD groups compared with the no CVD group in the Japanese participants. Among these GLP-1 RAs, dulaglutide was used most frequently, followed by liraglutide and semaglutide. It is noteworthy that, in other countries, dulaglutide is approved at doses of 0.75 mg and 1.5 mg, with the latter providing CV benefits, while, in Japan, only the 0.75 mg dose is approved [8, 44, 45]. Furthermore, whereas liraglutide 1.8 mg, the dose approved for benefitting CV outcomes, was already in use in other countries [5, 46, 47], Japan did not grant approval until May 2019 [48], concurrent to the CAPTURE study. Subcutaneous semaglutide improved CV outcomes at doses of 0.5 mg and 1.0 mg in patients with T2D (post hoc analysis) [49], and was approved in Japan in 2018 [50]. Higher-dose GLP-1 RAs, which possess proven CV benefits, are relatively new in Japan, and therefore, presumably, the usage of such GLP-1 RAs for patients with CVD was limited at the time of the study and may have subsequently increased.

In contrast to the use of GLP-1 RAs, the use of SGLT-2is in Japanese participants was higher compared with the global population [17]. However, the use of SGLT-2is with beneficial CV outcomes was lower in the CVD and ASCVD groups compared with the no CVD group in the Japanese participants. The most commonly used SGLT-2i with CV benefit was empagliflozin, followed by canagliflozin and dapagliflozin. SGLT-2is such as ipragliflozin, luseogliflozin, and tofogliflozin, which are prescribed in Japan for patients with T2D [51–54], have not been investigated in CVOTs for patients with CVD or at high risk of CVD.

As reported in analyses of CVOTs with Asian participants, Asians with T2D might have greater CV benefits from SGLT-2is and GLP-1 RAs compared with Caucasians [11]. The low use both of GLP-1 RAs and of SGLT-2is in patients with CVD and ASCVD–the risk-treatment paradox–(which results in high morbidity and mortality in patients with T2D [20]) may suggest a lack of awareness of their proven CV benefits among physicians; however, physicians in Japan may gradually increase the use of these GLAs if the benefits are more widely known.

Our analysis adds to the few published studies that provide an overview of medications prescribed for T2D in Japan. Our results on the pattern of GLA usage in Japan are similar to those of the retrospective analyses of the Japan Diabetes compREhensive database project based on an Advanced electronic Medical record System (J-DREAMS) database, which analyzed the prevalence of comorbidities and complications in Japanese patients with T2D [55]. According to this study, despite the presence of comorbidities and complications, patients with T2D in Japan mainly received DPP-4is (37.2%) and biguanides (36.1%) in referral centers. In addition, GLP-1 RAs (7.0%) and SGLT-2is (12.6%) were not widely prescribed in Japan for the management of T2D [55]. It is possible that Japanese doctors might prescribe GLP-1 RAs and SGLT-2is anticipating not only secondary prevention of CVD but also as primary prevention for participants without CVD, due to the results from some CVOTs [5–10]. There is a strong need to explore the expanded use of these antidiabetic agents within Japan.

With regard to CVD medication usage, the CAPTURE study reported that statin use was lower in Japanese participants (35.3%) compared with global participants (51.0%) [17]. According to the JCS–JDS consensus report, statins are recommended for patients with T2D and CVD to achieve target low-density lipoprotein-cholesterol (LDL-C) of < 100 mg/dL, which is higher than the recommendation by the EASD guidelines (< 50 or < 75 mg/dL) [12, 15]. The statin use in this CAPTURE Japan analysis was consistent with the reported mean LDL-C levels of < 100 mg/dL in the CVD and ASCVD subgroups.

The Japanese clinical practice guideline recommends adopting a treatment strategy for patients with diabetes based on their characteristics and disease severity [14]. The majority of the Japanese participants in the CAPTURE study belonged to the age group 65–75 years. The mean age of the participants from Japan was comparable with that of the global participants, while their mean BMI was lower versus the global study participants [17]. It is important to note that the BMI of Asian populations is generally lower than that of Caucasians [56]. When diabetes medication usage was analyzed by BMI, an increased use of biguanides, SGLT-2is, and GLP-1 RAs was observed with increasing BMI. Furthermore, various studies have also reported greater weight loss due to SGLT-2is and GLP-1 RAs compared with placebo [9, 10, 57], which is likely to impact upon physicians' decisions to prescribe these medications. When diabetes medication usage was analyzed by age, DPP-4is were the most prescribed medication in patients > 65 years. This may be related to DPP-4is being beneficial in controlling HbA1c levels in elderly patients with T2D with fewer side effects compared with other GLAs [58, 59]. Moreover, it was found that use of antidiabetic agents differed in participants according to their age, both in those with and those without CVD.

The present analysis has certain limitations. Japan has a unique healthcare system that includes clinic care and hospital healthcare systems [60]. The majority of the Japanese doctors participating in the CAPTURE study were diabetologists, which may have resulted in some bias. Hence, the data from Japanese centers cannot be directly compared with the global CAPTURE study due to differences in the healthcare settings. Since the prescribing pattern for use of GLAs in Japan seems to be governed by factors such as age, BMI, and comorbidities, without a specific guideline recommendation to use GLAs with proven CV benefit in patients with T2D, the findings may not be comparable with the global prescribing patterns. Although broad inclusion criteria were applied to ensure that the study sample was representative of the general adult T2D population, there were differences in age, antidiabetic agents used, and the prevalence of CVD between this cohort and other large Japanese cohort studies [26, 55, 61]. In addition, the sample size in this analysis was small ($n = 800$). As such, the generalization of our findings across the overall T2D population in Japan is a potential limitation of this analysis.

In conclusion, the present secondary analysis of the CAPTURE study provided a comprehensive overview of prescription patterns for the treatment of T2D in Japan. The analysis indicated that GLA usage in Japan differed from other countries. The overall use of GLAs with proven CV benefit was low, and comparable in participants with and without CVD in Japan; these findings are in line with those from the entire cohort of participants enrolled in the

CAPTURE study [17]. Increased education, new evidence and updates to guidelines on the management of diabetes may enhance the use of GLAs with proven CV benefit.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13340-023-00638-w.

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Author contributions YO, SS, and HS were investigators in the study and collected data. TS and KN contributed to statistical analyses required for the Japan data. All authors reviewed and edited drafts of the manuscript prior to submission. The authors confirm that they meet the International Committee of Medical Journal Editors uniform authorship requirements and that they have contributed to critical analysis and interpretation of the data, critically revised the article, and share in the final responsibility for manuscript content, as well as the decision to submit it for publication.

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Data availability Upon reasonable request, the datasets used and/or analyzed during the current study are available from the lead author.

Declarations

Conflict of interest YO has received honoraria/lecture fees from Novo Nordisk Pharma Ltd. and Sumitomo Pharma. SS has received honoraria/lecture fees from Eli Lilly Japan K.K., Novo Nordisk Pharma Ltd. and Sumitomo Pharma. KE and TS are employees of Novo Nordisk. KN holds shares in and is an employee of Novo Nordisk. HS has received research funding from Astellas Pharma Inc., Taisho Toyama Pharmaceutical, Takeda Pharmaceutical, Novo Nordisk Pharma, Sanofi, Mitsubishi Tanabe Pharma Co., Novartis Pharma K.K., Shionogi Pharma Co. Ltd., Boehringer Ingelheim, AstraZeneca K.K., and MSD; and honoraria from Shionogi Pharma Co., Mitsubishi Tanabe Pharma Co., Astellas Pharma Inc., Novartis Pharma K.K., Eli Lilly, Ono Pharmaceutical Co., MSD, and Sanofi.

Ethical approval The protocol was approved by the IEC or other appropriate body and was provided by each investigator prior to undertaking any study-related activities. Specifically, the protocol was approved by: Institute for Adult Diseases, Asahi Life Foundation Institutional Review Board (approval date: 03 Dec 2018; approval number: 11000766); Medical Corporation Ichi YouKai Institutional Review Board Makato Honda Board (approval date: 13 Feb 2019; approval number: 14000077); Seino Naika Clinic Chairman, Ethical Review Board (approval date: 15 Dec 2018; approval number: 18000150); Shinagawa East One Medical Clinic Ethical Review Board Shinagawa East One Medical Clinic (approval date: 26 Nov 2018; approval number: 11000993); Nihonbashi Sakura Clinic Institutional Review Board (approval date: 05 Dec 2018; approval number: 11001007); Heiwadai Hospital Institutional Review Board (approval date: 21 Nov 2018; approval number: 11000861); Jinnouchi Hospital Ethical Review Board (approval date: 10 Dec 2018; approval number: 16000034); Kouhoukai Ethical Committee (approval date: 03 Dec 2018; approval number: 18000145); Hospital Joint Institutional Review Board (approval date: 21 Dec 2018; approval number: 14000050); and Institutional Review Board for Considering the Ethics of Special Non-Profit Entity Clinical Trials (approval date: 28 Jan 2019; approval number: 12000065).

Human research All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent was provided by each participant prior to undertaking any study-related activities (during the first and only study visit).

Informed consent Informed consent was provided by each participant prior to undertaking any study-related activities (during the first and only study visit).

Approval date of registry and registration no. of the study/trial NCT03786406, 26 December 2018 and NCT03811288, 22 January 2019.

Authorship All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be submitted.

Prior presentation Some of the results from this study were previously presented at the 64th Annual Meeting of the Japanese Diabetes Society, virtual meeting, 2021.

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