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ORIGINAL ARTICLE

Effect of ipragliflozin on carotid intima-media thickness in patients with type 2 diabetes: a multicenter, randomized, controlled trial

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Aims To examine the effects of a 24-month treatment with ipragliflozin on carotid intima-media thickness (IMT) in type 2 diabetes patients.

Methods and results In this multicenter, prospective, randomized, open-label, and blinded-endpoint investigator-initiated clinical trial, adults with type 2 diabetes and haemoglobin A1C (HbA1c) of 6.0–10.0% (42–86 mmol/mol) were randomized equally to ipragliflozin (50 mg daily) and non-sodium-glucose cotransporter-2 (SGLT2) inhibitor use of standard-care (control group) for type 2 diabetes and were followed-up to 24 months. The primary endpoint was the change in mean common carotid artery IMT (CCA-IMT) from baseline to 24 months. A total of 482 patients were equally allocated to the ipragliflozin ($N = 241$) and control ($N = 241$) groups, and 464 patients (median age 68 years, female 31.7%, median type 2 diabetes duration 8 years, median HbA1c 7.3%) were included in the analyses. For the primary endpoint, the changes in the mean CCA-IMT from baseline to 24 months were 0.0013 [95% confidence interval (CI), −0.0155–0.0182] mm and 0.0015 (95% CI, −0.0155–0.0184) mm in the ipragliflozin and control groups, respectively, with an estimated group difference (ipragliflozin-control) of −0.0001 mm (95% CI, −0.0191–0.0189; $P = 0.989$). A group difference in HbA1c change at 24 months was also non-significant between the treatment groups [−0.1% (95% CI, −0.2–0.1); $P = 0.359$].

Conclusion Twenty-four months of ipragliflozin treatment did not affect carotid IMT status in patients with type 2 diabetes recruited in the PROTECT study, relative to the non-SGLT2 inhibitor-use standard care for type 2 diabetes.

Keywords Atherosclerosis • Carotid intima-media thickness • Ipragliflozin • Type 2 diabetes

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Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are one of the newer glucose-lowering agents that uniquely decrease plasma glucose levels via increased urinary glucose excretion.[1] According to the cardiovascular benefits beyond its glucose-lowering effect observed in the recent cardiovascular outcome trials (CVOTs) with SGLT2 inhibitors, the most recent treatment guidelines for type 2 diabetes recommend the agents to be considered preferentially in patients with type 2 diabetes at high risk of cardiovascular events or with established atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF), independent of their glycaemic status and preceding medications.[2,3] In these CVOTs, SGLT2 inhibitors robustly reduced the risk of hospitalization for HF, while they had neutral effects on the incidence of individual ASCVD.[4,5] In several experimental models, treatment with SGLT2 inhibitors has proved to attenuate atherosclerotic progression through improvement in insulin resistance and inflammatory status.[6–10] However, only some clinical evidence on the anti-atherosclerotic effect of SGLT2 inhibitors was available previously, at least at the time of planning and conducting the present study, and it is still controversial whether SGLT2 inhibitors could reduce the progression of atherosclerosis in clinical settings.[11–13]

We herein report the findings obtained from an investigator-initiated, multicenter, and randomized clinical trial that examined the vascular effects of 24-months of treatment with ipragliflozin, which is a first in a class of SGLT2 inhibitors in Japan, on carotid atherosclerosis assessed as intima-media thickness (IMT) in patients with type 2 diabetes.

Methods

Study design

The PROTECT (prevention of atherosclerosis by SGLT2 inhibitor: a multicentre and randomized controlled study) was a multicenter, prospective, randomized, open-label, and blinded-endpoint investigator-initiated clinical trial (UMIN000018440). After the study protocol was approved by the local institutional review boards at all sites, participant recruitment was conducted between September 2015 and June 2018 at 39 clinical sites throughout Japan. Prior to enrollment, all participants received an adequate explanation of the study plan and provided written informed consent. The trial was conducted in full compliance with the Declaration of Helsinki and according to the ethical guidelines and human research regulations in Japan.

After confirming the eligibility and reviewing the medical background, the patients were allocated equally to receive ipragliflozin (50 mg once daily) or non-SGLT2 inhibitor use of standard care (control) for type 2 diabetes. All patients were followed up over 24 months after the baseline visit. The complete protocol is described in Supplementary material online, *Method S1* and the details of the study rationale and design have been described previously.[14]

Study population

The detailed inclusion and exclusion criteria for the study are listed in Supplementary material online, *Table S1*. In brief, individuals eligible for the study were adults (≥20 years of age) who had haemoglobin A1c (HbA1c) of 6.0–10.0% despite diet and exercise therapy and/or taking standard diabetes medications for at least 3 months prior to randomization. Key exclusion criteria were individuals with type 1 diabetes, severe renal dysfunction [estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2], history of ASCVD within the 3-month period prior to the assessment of eligibility, HF with New York Heart Association functional classification III and IV, and history of administration of SGLT2 inhibitor 1 month prior to the study initiation.

Randomization and follow-up

Patients were randomly allocated to an ipragliflozin group or control group in a 1:1 ratio at the automatic web-based PROTECT Data Center. The randomization was performed using a web-based minimization method with a biased-coin assignment balanced for age (<65 and ≥65 years), HbA1c level (<7.0% and ≥7.0%), systolic blood pressure (BP, <135 and ≥135 mm Hg), use of statins, and use of metformin at the time of screening.

The observation period was set at 24 months after initiation of the study protocol. In principle, all participants were managed and treated to achieve a personalized goal recommended by the latest treatment guideline for type 2 diabetes in Japan. Subsequently, the participants who were assigned to the ipragliflozin group were administered 50 mg of ipragliflozin once daily in addition to their background medical therapy, and up-titration to 100 mg once daily was allowed in participants who did not achieve their glycaemic goals. Participants assigned to the control group continued their background therapy and medications for type 2 diabetes. The participant's background medical care, such as administration of glucose- and lipid-lowering agents, was unchanged during the study based on the clinical condition. In particular, it was prohibited to newly prescribed pioglitazone or changed its dose during the study due to a suppressive effect on the progression of carotid IMT.[15]

Study endpoints

The primary endpoint was the between-group difference in the change in mean IMT of the common carotid artery (CCA-IMT) from baseline to 24 months. The key secondary endpoints included the between-group difference in the changes in the other carotid IMT-related parameters [mean IMT of the bulb and internal carotid artery (ICA); max IMT of the CCA, bulb, and ICA; overall mean of mean IMTs of the CCA, bulb, and ICA; and overall mean of max IMTs of the CCA, bulb, and ICA] from baseline to 24 months and vital signs and laboratory measurements, including glycaemic, lipid, and renal parameters, over 24 months. In addition, information on adverse events was collected during the study period, as reported by the local investigators.

Measurements of carotid intima-media thickness

The protocol and method for measuring carotid IMT have been described in detail previously.[14,16] Briefly, carotid artery ultrasonography for imaging IMT was performed at baseline and after 24 months (or at premature termination) at each local site in a blinded manner by an expert, according to the testing manual (Supplementary material online, *Method S2*), as per the consensus statement by the American Society of Echocardiography.[17] Subsequently, all the imaging data were stored as JPEG files and sent to the core imaging laboratory, where an expert analyser measured the IMT values in a blinded manner using an automated IMT measurement software program (Vascular Research Tools 5, Medical Imaging Applications LLC, Coralville, IA, USA).

The mean and max CCA-IMT obtained from longitudinal B-mode images on the left and right sides were determined at the continuous region at 10 mm proximal to the origin of the bulb at the far wall using an auto-tracing system and then averaged over both sides at baseline and 24 months. The changes from baseline to 24 months were calculated for each side and averaged. The mean and max IMTs of the bulb and ICA were also measured in a similar manner.

Power calculation

Prior to the study initiation, no information on the effect of SGLT2 inhibitors on carotid IMT was available.[14] In the previous CHICAGO trial,[15] the mean IMT change was −0.001 mm in the pioglitazone group and + 0.012 mm in the glimepiride group at 72 weeks. We then hypothesized that ipragliflozin inhibited the progression of CCA-IMT at a level similar to that of pioglitazone and assumed that the change in CCA-IMT

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was −0.001 in the ipragliflozin group and +0.015 in the control group at 24 months, resulting in a difference of 0.016 with a standard deviation of 0.06; thus, the minimum required sample size was 222 patients per group with a total of 444 patients to detect a difference between the two groups at a 5% level with 80% power (two-sided). Considering a possible drop-out of ∼5% of the participants, the target number of patients for enrollment was 240 patients per group.

Statistical analysis

The final version of the statistical analysis plan developed before database lock is shown in Supplementary material online, *Method S3*. All the efficacy analyses were conducted in the full analysis set (FAS), including all randomized participants who did not have any serious protocol violation and who received at least one study treatment and had at least one data on efficacy endpoint after randomization, in a modified intention-to-treat manner. As a sensitivity analysis, the primary endpoint was also assessed in the per-protocol set (PPS), excluding those with any of the following significant violations of the protocol requirements, such as violation of inclusion/exclusion criteria or prohibited concomitant drug use.

For the primary endpoint, the changes in mean CCA-IMT from baseline to 24 months and its 95% CI that was estimated by analysis of covariance using corresponding values at baseline, the allocation adjustment factors, and cites as covariates, were compared between the treatment groups. Prespecified subgroup analyses were also performed to explore the robustness of the primary endpoint. Changes in other efficacy endpoints from baseline to 24 months were also compared between the treatment groups for the primary endpoint. We did not impute missing data for the analyses. The number and incidence of adverse events were collected for each treatment group in the safety analysis population, which was randomized and had any data after randomization.

Summary statistics for the baseline characteristics are expressed as median (interquartile range) for continuous variables and frequencies and proportions for categorical data. All *P* values were two-sided with a level of significance of 5%, and a two-sided 95% CI was also calculated. There were no adjustments for multiple comparisons. All statistical analyses were performed using R 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria) software.

Results

Enrollment, follow-up, and baseline clinical information of participants

Between September 2015 and June 2018, a total of 488 patients were registered at 39 clinical sites in Japan, and 482 patients were equally allocated either to the ipragliflozin or control group (*Figure 1*). Among them, 205 patients (85.1%) in the ipragliflozin and 215 patients (89.2%) in control completed the study. Among the ipragliflozin arm, seven were increased to 100 mg daily during the follow-up interval, and most received the dose of 50 mg daily.

Within the modified intention-to-treat population (FAS: ipragliflozin, 232 patients and control, 232 patients), a total of 401 (86.4%) patients (ipragliflozin, 197 patients and control, 204 patients) were included in the analysis of the primary endpoint.

The baseline demographic and clinical characteristics of the FAS population are shown in *Table 1*. The median age was 68 years, and 70% were men. The median diabetes duration was eight years, and the median HbA1c was 7.3%. Demographic and clinical characteristics were well balanced between the two groups. Approximately 40% were undergoing cardiovascular secondary prevention measures.

Carotid intima-media thickness

The baseline mean CCA-IMT values were median 0.79 (0.705, 0.905) mm in the ipragliflozin group and 0.81 (0.70, 0.91) mm in the control group, respectively. The carotid IMT values at baseline and 24 months and changes from baseline to 24 months are summarized in Supplementary material online, *Table S2*. For the primary endpoint, the changes in the mean CCA-IMT from baseline to 24 months were 0.0013 (95% CI −0.0155–0.0182) mm in the ipragliflozin group and 0.0015 (95% CI −0.0155–0.0184) mm in the control group, with an estimated group difference (ipragliflozin-control) of −0.0001 mm (95% CI −0.0191–0.0189; $P = 0.989$) (*Figure 2*). This was consistent in the PPS population [ipragliflozin, 194 patients and control, 196 patients; an estimated group difference of −0.0023 mm (95% CI −0.0216–0.0171; $P = 0.820$)]. The treatment effect for the primary endpoint also did not differ among most pre-specified subgroups (Supplementary material online, *Figure S1*). In the subgroup which was undergoing statin therapy at baseline, relative to non-statin users, ipragliflozin treatment favored the primary endpoint ($P_{int.} = 0.025$). Secondary endpoints for other carotid IMT parameters are also shown in Supplementary material online, *Table S2*, with no significant difference in their changes from baseline to 24 months between the treatment groups.

Other clinical efficacy endpoints

Changes in clinical and laboratory measures at 12 and 24 months are shown in Supplementary material online, *Table S3*. The reduction in HbA1c in the ipragliflozin group was significantly larger at 12 months than that in the control group, while the difference between the treatment groups disappeared at 24 months. Ipragliflozin treatment reduced systolic and diastolic BP over 24 months, and the group difference in changes in systolic BP was significant at 24 months. Changes in fasting blood glucose, body mass index, high-density lipoprotein cholesterol, and uric acid in the ipragliflozin group over 24 months were significantly higher than those in the control group. Ipragliflozin also reduced eGFR over 12 months, while the level recovered approximately to the control level at 24 months.

Adverse events

For the safety analysis population (ipragliflozin 241 and control 240), 75 patients (31.1%) had one or more adverse events (total 76 events; severe 13 and moderate 24) in the ipragliflozin group and 68 (28.3%) (total 74 events; severe 15, and moderate 21) in the control group. Individual numbers of incident adverse events reported by the local investigator are summarized in Supplementary material online, *Table S4*. Regarding the adverse events of special interest (Supplementary material online, *Table S5*), all-cause deaths occurred in four patients (1.7%) in the ipragliflozin group and five patients (2.1%) in the control group; one patient died from HF in the ipragliflozin group, and two patients died from myocardial infarction (MI) in the control group. HF developed in three patients in the ipragliflozin group and two patients in the control group.

Discussion

In the PROTECT study for Japanese patients with type 2 diabetes, there was no difference in changes in carotid IMT parameters over 24 months between the treatment groups, despite obvious improvement of cardiometabolic status in patients treated with ipragliflozin. This suggests that the anti-atherosclerotic effect is less predominant among the cardiovascular benefits of SGLT2 inhibitor observed in the recent CVOTs, at least within this observation period after initiation of drug administration.

SGLT2 inhibitors are known to cause multifaceted haemodynamic and metabolic actions, originating from primary natriuresis and osmotic diuresis beyond the glucose-lowering effect.[18] Considering these pharmacological effects, treatment with SGLT2 inhibitors has the potency to favourably affect the cardiometabolic status and reduce the risk of cardiovascular events. Especially, the haemodynamic

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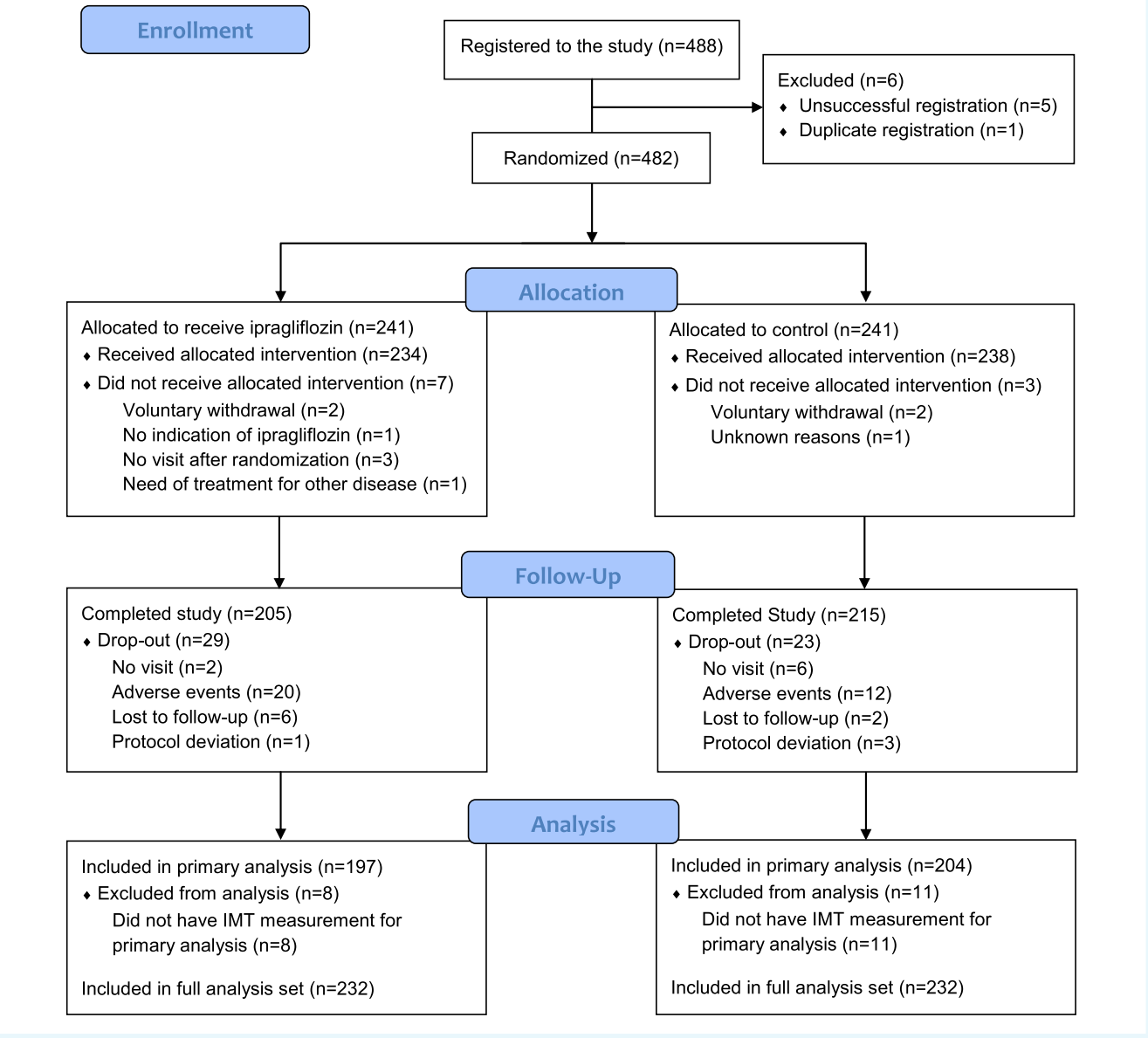

Figure 1 Flow diagram of participants in the PROTECT study. IMT, intima-media thickness.

actions are prone to be a key driver of cardio- and nephroprotective effects of SGLT2 inhibitors,[19,20] possibly contributing to the reduction in the risk of HF-related and renal events. On the other hand, the vascular effects of SGLT2 inhibitors and the impact of atherosclerosis are not completely elucidated.

To date, three clinical studies have examined the effects of SGLT2 inhibitors on the burden of atherosclerosis as assessed by carotid IMT in patients with type 2 diabetes. In the FUSION study, a 52-week of ipragliflozin treatment did not affect CCA-IMT in 134 Japanese patients with type 2 diabetes,[11] seemingly to be a comparable trend to our findings. However, their study was a non-randomized, single-arm design. Irace *et al.*[12] reported that a 3-month empagliflozin treatment was associated with an attenuation of CCA-IMT. Nevertheless, it was a non-randomized prospective cohort study with a smaller sample size (20 patients treated with empagliflozin), shorter observational duration, and no comparison with the reference arm. In the randomized UTOPIA study,[13] a 104-week of tofogliflozin treatment significantly reduced the mean and maximum CCA-IMTs in 169 Japanese patients with type 2 diabetes who were undergoing primary prevention measures for ASCVD, similar to that with the conventional treatment in the control arm, resulting in the non-significant group differences. Thus, the effects of SGLT2 inhibitors on carotid IMT progression are still controversial, and its detailed reasons are currently uncertain.

Compared with these previous studies, there were several differences in the study design and population in the PROTECT study. Especially a partial discrepancy in the effects of SGLT2 inhibitors on carotid IMT might be explained at least partly by different study populations. The PROTECT participants were older (median 68 years) than those in other studies (mean age: 54 years in FUSION, 58 years in the study by Irace *et al.*, and 61 years in UTOPIA). Additionally, the prevalence of the previous history of ASCVD in PROTECT was high (39.2%) relative to others (27.2% in FUSION and 0% in UTOPIA; not provided in the study by Irace *et al.*). Previous studies suggested that the inhibitory effect of other classes of anti-diabetes agents such

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Table 1 Baseline demographic and clinical characteristics

Variable	Overall ($n = 464$)	Ipragliflozin ($n = 232$)	Control ($n = 232$)
Age,[a] year	68 (60, 73)	67 (60, 72)	68 (60, 73)
Sex			
Women	147 (31.7)	71 (30.6)	76 (32.8)
Men	317 (68.3)	161 (69.4)	156 (67.2)
Current smoker	94 (20.3)	47 (20.3)	47 (20.3)
BMI, kg/m^2	25.8 (23.4, 29.0)	25.3 (23.7, 28.9)	26.2 (23.2, 29.2)
Systolic BP,[a] mm Hg	130 (122, 141)	130 (120.5, 140)	130 (122, 141)
eGFR, mL/min/1.73 m^2	68.42 (58.93, 79.65)	68.75 (59.85, 77.16)	67.73 (58.29, 82.08)
Diabetes duration,[b] year	8.0 (3.9, 14.0)	8.5 (4.9, 14.0)	7.5 (3.7, 13.0)
HbA1c,[a] %	7.3 (6.8, 7.9)	7.2 (6.8, 7.9)	7.3 (6.7, 7.9)
Medical history			
Hypertension	298 (64.2)	148 (63.8)	150 (64.7)
Dyslipidaemia	289 (62.3)	146 (62.9)	143 (61.6)
ASCVD	182 (39.2)	95 (40.9)	87 (37.5)
HF and/or cardiomyopathy[c]	26 (5.6)	12 (5.2)	14 (6.0)
Prior medication			
ACE inhibitor	81 (17.5)	40 (17.2)	41 (17.7)
ARB	208 (44.8)	95 (40.9)	113 (48.7)
Calcium channel blocker	228 (49.1)	110 (47.4)	118 (50.9)
β-blocker	141 (30.4)	70 (30.2)	71 (30.6)
Statin[a]	309 (66.6)	153 (65.9)	156 (67.2)
Anti-platelet	193 (41.6)	92 (39.7)	101 (43.5)
Insulin	20 (4.3)	9 (3.9)	11 (4.7)
Metformin[a]	166 (35.8)	81 (34.9)	85 (36.6)
Sulfonylurea	105 (22.6)	46 (19.8)	59 (25.4)
Thiazolidinedione	46 (9.9)	24 (10.3)	22 (9.5)
DPP-4 inhibitor	285 (61.4)	145 (62.5)	140 (60.3)
GLP-1 receptor agonist	9 (1.9)	5 (2.2)	4 (1.7)

Data are presented as median (interquartile range) or number (percentage).
[a]Data at randomization.
[b]Data were available for 183 patients each in the ipragliflozin and control groups.
[c]Investigator reported.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HF, heart failure.

as dipeptidyl peptidase-4 inhibitor on carotid IMT progression was obvious in patients with type 2 diabetes receiving primary prevention for ASCVD, while less in those undergoing secondary prevention measures.[21] Thus, the therapeutic effects of glucose-lowering interventions on carotid IMT may be different in patients with type 2 diabetes according to the ASCVD status. On the other hand, the statin-naïve population (33.4%), relative to the statin-user, was likely to receive a beneficial impact of ipragliflozin treatment on carotid IMT progression in this study. Since statin has established effects on delaying carotid IMT progression,[22] the atherogenicity of carotid IMT in the statin-users might have been stable prior to the study enrollment.

In the CVOTs for patients with type 2 diabetes and at high risk of cardiovascular events, treatment with SGLT2 inhibitors, relative to placebo, reduced the risk of major adverse cardiovascular events (MACEs); nevertheless, there was no significant reduction in the risk of individual ASCVD and components of MACE in each CVOT.[4,5] This may partly explain our findings of no effect on carotid IMT change as a therapeutic marker on atherosclerosis. In several meta-analyses, SGLT2 inhibitors also had no effect on the risk of stroke, while the treatment modestly reduced the risk of MI.[4] Considering the haemodynamic actions and erythropoiesis of SGLT2 inhibitors, a favourable modification of myocardial oxygen demand and supply balance, rather than attenuation of atherosclerotic burdens, was likely to be a key mechanism of the reduced risk of MI.[23] However, the reasons for this inconsistency between the impact on the incidences of stroke and MI are poorly understood. Effects on atherosclerotic lesions in other arteries are also uncertain. Further studies are needed to assess whether or how SGLT2 inhibitors affect atherosclerosis and the risk of ASCVD.

The usual dose of ipragliflozin, the first SGLT2 inhibitor released in Japan in 2014, is 50 mg daily. As in this study, most patients also had received that dose in a post-marketing surveillance study of ipragliflozin for Japanese patients with type 2 diabetes.[24] In that observational study, ipragliflozin induced a significant and sustained reduction in HbA1c for 36 months, and its change from baseline at 36 months was $-0.66 \pm 1.25\%$. Compared with it, the reduction in HbA1c in our study was a bit modest. Although the precise reason for that is unclear, a relatively lower baseline HbA1c level in our study than

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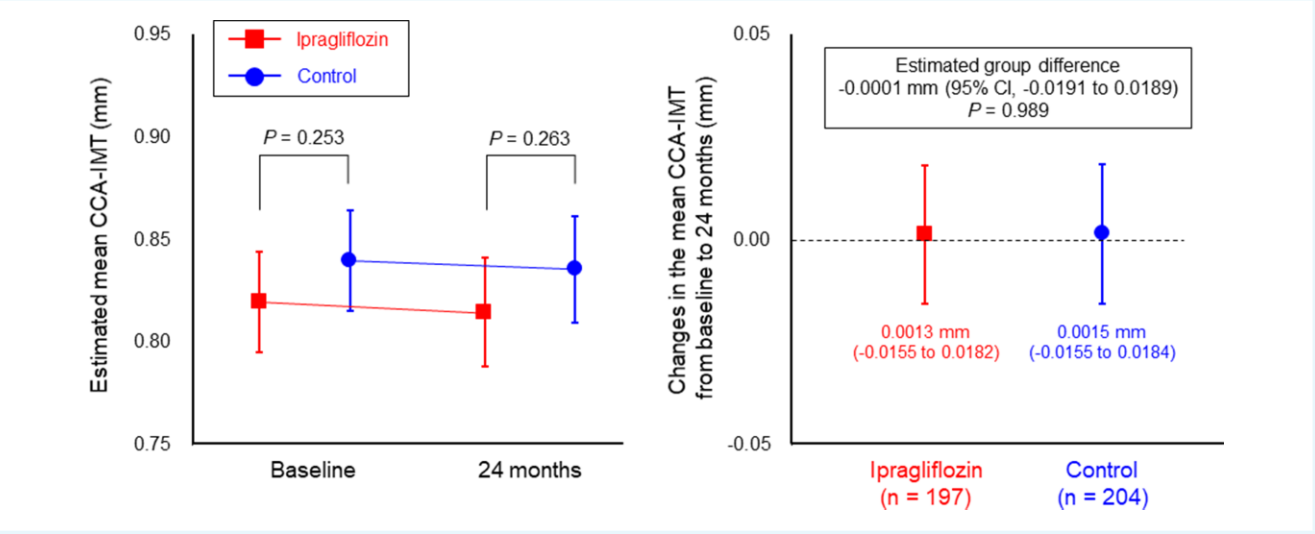

Figure 2 Changes from baseline at 24 months in the mean common carotid artery - intima-media thickness. The left panel shows the estimated mean common carotid artery - intima-media thickness values at baseline and 24 months. The right panel shows the changes in the mean common carotid artery - intima-media thickness from baseline to 24 months and its estimated group difference, a primary endpoint of the study. The error bars mean the 95% confidence interval. CCA, common carotid artery; CI, confidence interval. For other abbreviations, see *Figure 1*.

in that study might have influenced the efficacy of lowering HbA1c. It also remains to be determined whether such modest changes in HbA1c had an impact on the course of carotid IMT status in the PROTECT study.

Study limitations

This study has several limitations. First, this was an open-label study rather than a double-blinded one, and accordingly, unexpected bias towards the study endpoints could have occurred. To minimize this possibility, carotid IMT tests at each local site and measurements of the parameters at a central core laboratory were conducted by skilled technicians in a blinded manner. Additionally, the investigator's choice of therapy might have affected several efficacy endpoints. Although there were requirements that the background cardiometabolic drugs that can affect carotid IMT remained unchanged during the study interval, there were minor changes in the prescription frequency of some medications for diabetes and dyslipidaemia at 24 months in both treatment groups (Supplementary material online, *Table S6*). Hence, we cannot exclude the possibility that those changes in concomitant medications affect the efficacy endpoints, including carotid IMT and HbA1c, but the effects are expected to be relatively small. Second, the sample size might have been extremely small to detect a minute treatment effect on carotid IMT progression observed in the present study. Although the recruitment reached at least the minimum required number (222 per arm) to detect an estimated treatment effect on carotid IMT between the treatment groups with 80% power, the final number of patients for whom the carotid IMT data on the primary endpoint was available was below the planned number. Third, the progression rate of CCA-IMT, as expected while designing the study, was not observed in the control group. This might have resulted from an overestimation of the extent of carotid IMT progression in this relatively lower-risk Asian patient population compared with Western populations,[25] and in the contemporary clinical setting where evidence-based cardiometabolic medications that have a potency to cause a beneficial impact on atherosclerosis are often on treatment. Therefore, it is unclear whether the present findings are applicable to other ethnicities and patient populations in different medical situations. Additionally, it remains to be clarified whether the findings observed herein depend on ipragliflozin or the study population and setting. Finally, there is an active controversy on the clinical relevancy between the carotid IMT progression and subsequent risk of cardiovascular events.[26,27] More suitable surrogate markers and endpoints may be required to reflect interventional effects on this relevancy better.

Conclusions

Twenty-four months of ipragliflozin treatment, relative to the standard care for type 2 diabetes without SGLT2 inhibitor use, did not affect carotid IMT progression in patients with type 2 diabetes who were recruited in the PROTECT study. Our findings suggest that anti-atherosclerotic effect is less predominant among the cardiovascular benefits of SGLT2 inhibitors, at least within this treatment period. Although our findings currently do not support the use of SGLT2 inhibitors for delaying atherosclerosis in patients with type 2 diabetes, further research is warranted to determine the long-term effects of atherosclerosis and the impact of SGLT2 inhibitors on relevant cardiovascular events.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Author contributions

A.T. participated in the study design, operations, analysis, and interpretation of data and drafted the paper. M.S., Y.O., H.T., K.E., M.S., H.M, I.T., K.M., Y.K., T.I., S.U., T.M., and K.N. contributed to the study concept and design, study operations, data collection, analysis and interpretation of data, and critically reviewed and edited the paper. H.Y. contributed to the statistical analysis and figure preparation. T.I. was responsible for IMT evaluation. M.K. helped to steer the study as a research advisor and reviewed and edited the draft paper. T.M. and K.N. were principal investigators of the PROTECT study, and all authors take responsibility for the integrity of the data and the accuracy of data analysis.

Data availability

The data are available for secondary analysis upon reasonable request from researchers who submit a detailed proposal outlining their intended use of the data and after approval by the principal investigators and the steering committee of the PROTECT study. Inquiries are to be addressed to the corresponding authors.

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