Ipragliflozin lowers small, dense low-density lipoprotein cholesterol levels in Japanese patients with type 2 diabetes mellitus

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A B S T R A C T
Aims: This preliminary randomized, parallel-group comparative study evaluated the efficacy of ipragliflozin for reduction of small dense low-density lipoprotein cholesterol (sd LDL-C) levels in Japanese patients with type 2 diabetes mellitus (T2DM).

Methods: Sixty-two patients with T2DM (age, 56±8 years; hemoglobin A1c levels, 8.1±0.9%; BMI, 27.5±3.3 kg/m²) were randomly assigned in a 2:1 ratio to receive ipragliflozin (50 mg/day) (treatment group; n = 40) or continued treatment (control group; n = 22) for 12 weeks.

The primary endpoints were changes in sd LDL-C levels detected using the LipoPhor AS® system; the secondary endpoints included changes in the sd LDL-C/large buoyant LDL-C (lb LDL-C) ratio, a surrogate marker for LDL particle size, and percent changes in routine lipid parameters.

Results: The treatment group exhibited a statistically significant reduction from baseline for LDL-C levels (-0.37 mg/dL vs. 14.4 mg/dL, p = 0.038), sd LDL-C levels (-1.28 mg/dL vs. 2.81 mg/dL, p = 0.012), and sd LDL-C/lb LDL-C ratio (-3.20% vs. 4.58%, p = 0.040) compared with the control group. Multiple regression analysis among all subjects revealed change in TG levels (p = 0.011) and LDL-C levels (p = 0.024) as well as change in body weight (p = 0.006) as independent factors contributing to the reduction in sd LDL-C.

Conclusions: Ipragliflozin may have a potential for lowering sd LDL-C levels associated with increasing LDL particle size in Japanese patients with T2DM.

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Introduction

Type 2 diabetes mellitus (T2DM) is associated with a substantially increased cardiovascular (CV) risk [1], and several international guidelines statements addressing T2DM management [2,3] underscore the need to prevent and reduce CV complications.

In light of the multi-faceted pathogenesis of CV disease in diabetes, it would be advantageous for a specific pharmaceutical intervention to attenuate atherosclerosis risk multi-dimensionally and beyond glycemic control alone [4]. The potential effect of such interventions on CV risk might ultimately depend on the drug’s mode of action in terms of the CV pathway being modulated. However, to date, the potential effects of specific glucose-lowering agents – that is, sulphonylurea (SU), glinides, metformin, thiazolidinediones, insulin, glucagon-like peptide-1 receptor analogs, or dipeptidyl-peptidase-4 (DPP-4) inhibitors – on CV events in patients with T2DM remain uncertain [5], although some agents, such as metformin and pioglitazone, have been reported to reduce major cardiovascular events in a limited number of newly diagnosed low-risk obese patients (n = 342) with T2DM [6] or to reduce the risk with marginal significance (p = 0.027) in high-risk patients with T2DM [7], respectively.

Sodium glucose cotransporter-2 (SGLT-2) inhibitors are a new class of glucose-lowering agents that reduce hyperglycemia in patients with T2DM by limiting renal glucose reabsorption; as a result, they increase urinary glucose excretion (UGE) [8]. Since SGLT-2 inhibitors’ mode of action is independent of insulin secretion, these agents are associated with a low risk of hypoglycemia, which has been linked to increased CV events [9]. In addition, they have been demonstrated to correct post-prandial glucose level [10], improve insulin sensitivity [11], reduce systolic and diastolic blood pressure without a compensatory increase in heart rate [12], decrease body weight mainly due to reduction in visceral or subcutaneous fat mass [8], and reduce urinary albumin excretion [13] and serum level of uric acid [14], all of which are potential or established CV risk factors. In the recent EMPA-REG outcomes trial, empagliflozin, an SGLT-2 inhibitor, reduced the rates of death from cardiovascular causes, hospitalization for heart failure, and death from any cause.

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by more than 30% in patients with T2DM at a high risk of cardiovascular disease during 3.1 years [15]. However, the preventive mechanisms are not yet known.

In this context, regarding dyslipidemia, which are well-known established CV risk factors, SGLT-2 inhibitors are associated with a small increase in HDL-C as well as an increase in LDL-C with concomitant reductions in triglyceride (TG) levels [16,17]. Whether these small lipid changes are clinically relevant and whether they could potentially affect total CV risk requires further clarification.

Although statin therapy targeting a reduction in LDL-C decreases the risk of coronary heart disease (CHD) and all-cause mortality, a substantial number of cases of CHD are not prevented and residual risk factors remain unclear, stimulating the search for a secondary treatment target [18].

Compared with large buoyant LDL (lb LDL), small dense LDL (sd LDL) are thought to be more atherogenic as a result of their better penetration of the arterial wall, lower binding affinity for the LDL receptor, longer plasma half-life, and weaker resistance to oxidative stress [19]. Several studies have reported a two- to three-fold increase in CHD risk in patients with sd LDL [20]. In particular, sd LDL is reportedly predominant in patients with T2DM [21], a well-known independent risk factor for coronary artery disease [22].

Ipragliflozin (ASP1941; Astellas Pharma Inc. Tokyo, Japan and Kotobuki Pharmaceutical Co., Ltd, Nagano, Japan) is a novel and select SGLT2 inhibitor and is one of the first published C-aryl glycoside compounds (as opposed to the labile ortho-attachment of O-glycoside molecules seen in in vivo conditions) [23]. In a recently implemented, randomized, double-blind, placebo-controlled study using 129 Japanese patients with T2DM, 50 mg ipragliflozin once daily has been associated with a significant elevation in HDL-C levels (+2.7 mg/dL) with a concomitant small non-significant decrease in TG levels (−12.3 mg/dL) as well as no increase in LDL-C levels (−1.4 mg/dL) [24].

Here, we conducted a preliminary open-label, randomized, parallel-group comparative study evaluating the efficacy of 50 mg ipragliflozin once daily for reduction of sd LDL-C levels and sd LDL-C/lb LDL-C ratios from baseline between the two treatment groups. The secondary endpoints were changes in mid-band LDL-C levels, mid-band LDL-C/lb LDL-C ratio, and the percent change of routine lipid parameters (LDL-C, total cholesterol, high-density lipoprotein cholesterol [HDL-C], triacylglycerides [TG], non HDL-cholesterol) from baseline between the groups. Other secondary endpoints included changes in Hba1c, glycated albumin levels, and body weight from baseline between the groups. Levels of lb LDL-C were calculated by subtracting sd LDL-C and mid-band LDL-C levels from total LDL-C. Levels of lb LDL-C estimated using this method were reported to be well correlated with the values determined by ultracentrifugation (r = 0.858, p < 0.0001) [25]. The sd LDL-C/lb LDL-C was calculated as a surrogate marker for LDL particle size [26]. To assess safety, the incidence and details of adverse events and laboratory abnormalities were investigated.

Compliance with treatment was assessed at 4, 8, and 12 weeks by interview. In principal, any change of the dosage regimen of concomitant anti-diabetes and antilipidemic drugs was prohibited during the study. Laboratory tests (including biochemistry tests, hematology tests, urinalysis, serum lipids, and other parameters) were performed after an overnight fast at randomization and 12 weeks after randomization when LDL-C subfractions were re-evaluated using the LipoPhor AS® system. All blood tests were performed using standard methods. LDL-C level was calculated using the Friedewald equation [27]. Non-high-density lipoprotein cholesterol (non-HDL-C) levels were calculated by subtracting the HDL-C level from the total cholesterol level. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). eGFR was calculated using the formula reported by Matsuo et al. [28]. Presence of diabetic retinopathy was evaluated by fundus examination performed by an ophthalmologist. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or current use of antihypertensive agents.

This study is registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; Japan), number UMIN0000014422.

**Polycrystalamine-gel disc electrophoresis (PAGE) and densitometric analysis**

PAGE was performed using a commercial kit (LipoPhor AS®; ASKA Co., Ltd., Kanagawa, Japan) [29]. Briefly, serum samples (25 μL) were added to 200 μL of the loading gel solution containing Sudan Black B and injected into a 3% polycrystalamide gel. The gel was photopolymerized for 30 min, and the loaded samples were electrophoresed for 25 min. The resulting electrophoresed patterns were scanned with a densitometer (Densitron Finger Printer; Jokoh, Japan), and the percentages of the area under the curve (AUC%) for the VLDL, LDL, and HDL peaks were calculated. The AUC% values of
mid-band LDL and sd LDL were identified according to a report by Mishima and colleagues [30,31] with slight modifications. First, the peak positions of VLDL and HDL were set as 0 and 1 (relative migration [Rm]), as shown in Fig. 1. Second, the scanned spectrum was overlaid with a control spectrum representing normal lipoprotein levels (Fig. 1). Finally, the presence or absence of sd LDL and mid-band LDL was determined by identifying the excess area in the spectrum of samples on either or both sides of the control LDL peak. If there were substantial areas for mid-band LDL and/or sd LDL, we used the AUC% of Rm > 0.40 and Rm 0.10–0.18 in the LDL peak as sd LDL and mid-band LDL, respectively. The LDL-C value calculated from the Friedewald equation multiplied by the respective AUC% was used as the calculated value of each LDL-C subfraction. The ratios (%) of sd LDL-C and mid-band LDL-C to total LDL-C were also determined.

Statistical analysis

Data are expressed as means ± standard deviation unless otherwise noted. Comparisons of discrete variable data were analyzed using the chi-squared test or Fisher’s direct test, as appropriate. Differences between two variables were examined for statistical significance using the two-tailed Student’s paired or unpaired t-test, as appropriate. Correlations between sets of two independent continuous variables were investigated using Spearman’s rank correlation coefficient method. Two-way repeated measures ANOVA with post-hoc Bonferroni tests were used to determine differences in parameter changes over the time.

Multiple linear regression analysis among all study subjects (n = 62) was conducted to determine the independent predictors of changes in sd LDL-C levels (Δsd LDL-C) and the sd LDL-C/lb LDL-C ratio (Δsd LDL-C/lb LDL-C ratio). All variables considered clinically meaningful parameters for a patient’s background were employed as independent variables in multivariate analysis (i.e., sex, age, change in BMI, diabetes duration, change in LDL-C, change in TG, and change in HbA1c). Δsd LDL-C, Δsd LDL-C/lb LDL-C ratio, change in BMI, LDL-C, TG, and HbA1c were all calculated as each level 12 weeks after starting ipragliflozin minus the baseline levels. For all tests, p < 0.05 was considered statistically significant. All the statistical analyses were performed using the JMP version 5.1 software (SAS Institute Inc., Cary, NC, USA).

Results

Subject characteristics and lipids at baseline

The mean ± standard deviation for age, BMI, HbA1c, and glycated albumin levels at baseline for all study subjects (n = 62) were 55.6 ± 7.7 years, 27.6 ± 3.3 kg/m², 8.1 ± 1.0%, and 19.5 ± 3.2%, respectively. The relative percentages of users of concomitant antihyperglycemic agents (sulphonylurea: metformin: DPP-4 inhibitors) and antihyperlipidemic agents (statin: fibrate: ezetimibe) at baseline among all study subjects were 56:82:74 and 79:7:5, respectively. The baseline clinical characteristics of subjects in the two groups (treatment group: n = 40; control group: n = 22) are presented in Table 1. The two groups were well matched according to gender, age, BMI, eGFR, ratio of statin use, and diabetes characteristics, including duration, baseline HbA1c, oral antihyperglycemic therapy, and complications as well as baseline lipid levels, including levels of total cholesterol, LDL-C, TG, sd LDL-C, mid-band LDL-C, and sd LDL-C/lb LDL-C ratio.

All patients completed the study protocol without any withdrawals due to treatment-related serious adverse events. Mean compliance was found to be ≥95% during the study period.

Changes in routine lipids parameters

There were no significant differences in the changes from baseline between the treatment and control groups for TG levels (133 ± 72→121 ± 60 mg/dL vs. 154 ± 71→157 ± 85 mg/dL, p = 0.42, respectively) and HDL-C levels (48 ± 9→50 ± 10 mg/dL vs. 45 ± 10→48 ± 10 mg/dL, p = 0.72). However, the treatment group exhibited a statistically significant decrease compared with the control group with respect to changes in total cholesterol levels (169 ± 38→165 ± 35 mg/dL vs. 171 ± 33→184 ± 36 mg/dL, p = 0.010), LDL-C levels (95 ± 31→91 ± 26 mg/dL vs. 95 ± 28→105 ± 30 mg/dL, p = 0.020), and non-HDL-C levels (122 ± 34→115 ± 30 mg/dL vs. 126 ± 31→136 ± 33 mg/dL, p = 0.010).

Similarly, there were no significant differences in changes from baseline between the treatment and control groups for the percent changes in TG levels (+2.2% vs. +11.7%, p = 0.50, respectively) and HDL-C levels (+6.2% vs. +8.2%, p = 0.60). However, the treatment group exhibited a statistically significant decrease compared with the control group with respect to the percent changes in total cholesterol levels (−1.3% vs. −9.2%, p = 0.011) and non-HDL-C levels (−3.5% vs. −10.8%, p = 0.012).

Changes in LDL-C and its subfractions (Fig. 2)

There were no significant differences in the changes from baseline between the treatment and control groups for mid-band LDL-C (+0.1 mg/dL vs. +1.94 mg/dL, p = 0.29) and lb LDL-C levels (−3.43 mg/dL vs. −4.91 mg/dL, p = 0.127). However, the treatment group exhibited a statistically significant reduction from baseline compared with the control group for LDL-C levels (−4.27 mg/dL vs.
Table 1
Baseline clinical characteristics of the study subjects with type 2 diabetes mellitus between the treatment and control groups

| Characteristic                        | Treatment group | Control group | P value |
|---------------------------------------|-----------------|---------------|---------|
| n                                     | 40              | 22            | ns      |
| Gender (male/female)                  | 26/14           | 22/12         | ns      |
| Age (years)                           | 54.8 ± 9.3      | 55.4 ± 7.5    | ns      |
| BMI (kg/m²)                           | 27.8 ± 3.9      | 27.3 ± 3.3    | ns      |
| Diabetes duration (years)             | 9.7 ± 4.6       | 9.5 ± 4.4     | ns      |
| HbA1c (%)                             | 8.1 ± 1.0       | 8.2 ± 1.1     | ns      |
| Concomitant antihyperglycemic agents SU/Met/DPP-4i (%) | 55/83/80    | 59/82/73     | ns      |
| Concomitant antihyperlipidemic agents (statin/fibrates/ezetimibe) (%) | 80/8/5        | 77/5/5        | ns      |
| Total cholesterol (mg/dL)             | 169 ± 38        | 171 ± 33      | ns      |
| LDL-cholesterol (mg/dL)               | 95 ± 31         | 92 ± 26       | ns      |
| Triglycerides (mg/dL)                 | 133 ± 72        | 154 ± 71      | ns      |
| HDL-cholesterol (mg/dL)               | 48 ± 9          | 45 ± 10       | ns      |
| Non-HDL cholesterol (mg/dL)           | 122 ± 34        | 126 ± 31      | ns      |
| Small-dense LDL-cholesterol (mg/dL)   | 2.9 ± 4.9       | 2.9 ± 4.4     | ns      |
| Large-buoyant LDL-cholesterol (mg/dL) | 82.0 ± 28       | 82.5 ± 26     | ns      |
| Mid-band LDL-cholesterol (mg/dL)      | 10.1 ± 6.0      | 10.0 ± 5.6    | ns      |
| Small-dense LDL-cholesterol/LDL-cholesterol ratio (%) | 1.8 ± 3.7 | 1.5 ± 2.0 | ns |
| Mid-band LDL-cholesterol/LDL-cholesterol ratio (%) | 6.2 ± 2.5 | 12.7 ± 6.5 | ns      |
| sd LDL-C/lb LDL-C ratio(%)            | 5.3 ± 16.0      | 6.1 ± 2.5     | ns      |
| eGFR (mL·min⁻¹·1.73m²⁻¹)              | 79.5 ± 14.9     | 76.1 ± 13.6   | ns      |
| Complications                         |                 |               |         |
| Retinopathy (n)                       | 5 (13%)         | 1 (5%)        | ns      |
| Hypertension (n)                      | 21 (53%)        | 13 (59%)      | ns      |
| Dyslipidemia (n)                      | 33 (83%)        | 18 (82%)      | ns      |

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; Met, metformin; DPP-4i, DPP-4 inhibitors; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; ns, not significant.

All values are means ± standard deviations or numbers of subjects with percentages in parentheses. P values between two groups of subjects were obtained using the unpaired t-test, chi-squared test, or Fisher’s direct test, as appropriate.

In addition, the treatment group exhibited a statistically significant reduction from baseline compared with the control group for the percent changes of LDL-C levels (−0.37% vs. +13.1%, p = 0.049), mid-band LDL-C levels (+0.05% vs. +1.91%, p = 0.025), sd LDL-C levels (−0.74% vs. +11.0%, p = 0.038), and sd LDL-C/lb LDL-C levels (−3.20% vs. +4.58%, p = 0.040).

A Spearman’s rank correlation analysis revealed a strong positive correlation between Δsd LDL and the Δsd LDL-C/lb LDL-C ratio among all study subjects (p < 0.0001), indicating that a reduction in sd LDL-C levels might be potently linked to an increase in LDL particle size.

Multiple linear regression analysis

The results of multiple linear regression analysis among all study subjects indicate that the factors contributing significantly to Δsd LDL-C were change in body weight (p = 0.006, r² = 0.183), change in TG (p = 0.011, r² = 0.069), and change in LDL-C (p = 0.024, r² = 0.076) (Table 2A). Sex, age, diabetes duration, and change in HbA1c were not significant predictors. Change in body weight, change in LDL-C, and change in TG together accounted for 32.8% of the total variance in Δsd LDL-C (Table 2A).

The results of the same analysis indicate that the factors contributing significantly to Δsd LDL-C/lb LDL-C ratio were change in TG (p = 0.002, r² = 0.213) and change in body weight (p = 0.022, r² = 0.102) (Table 2B). Sex, age, diabetes duration, change in HbA1c, and changes in LDL-C were not significant predictors. Change in body weight and change in TG together accounted for 31.5% of the total variance in the Δsd LDL-C/lb LDL-C ratio (Table 2B).

Changes in hemoglobin A1c, glycated albumin levels, and body weight

The treatment group exhibited a statistically significant decrease in hemoglobin A1c and glycated albumin levels compared with the control group 12 weeks after starting 50 mg ipragliflozin once daily (−0.61 ± 0.52% vs. +0.52 ± 0.74%, p < 0.0001 and −2.92 ± 2.48% vs. +0.89 ± 2.45%, p < 0.0001, respectively). The treatment group similarly exhibited a statistically significant decrease in body weight compared with the control group (−1.51 ± 1.28 kg vs. +0.45 ± 0.77 kg, p < 0.0001). Therefore, these glycemic and weight changes in response to the study drug are confounding factors in our study results. Changes in various clinical parameters other than...
lipids between the two treatment groups were shown in Table S1 in the Supplementary Appendix.

Discussion

Our present data revealed that administration of 50 mg ipragliflozin once daily provided a statistically significant reduction in the percent LDL-C levels, sd LDL-C levels, and sd LDL-C/lb LDL-C ratio compared with that in the control group. These results indicate that this compound may lower sd LDL-C levels associated with increasing LDL particle size. To the best of our knowledge, this is the first randomized control study to investigate the sd LDL-C-lowering effect of SGLT-2 inhibitors.

The predominance of sd LDL particles, which leads to the decrease of LDL particle size, has been reported to be associated with enhanced cardiovascular risk [32,33]; accordingly, sd LDL blood concentration is significantly higher in patients with T2DM or coronary artery disease than in healthy individuals [34]. Thus, the increase of LDL particle size accompanied by the decrease of sd LDL might represent a novel preventive therapeutic target beyond lipid-lowering itself, especially in patients with T2DM.

However, the LDL subfractionation methodology is an important issue, because there is substantial heterogeneity among the methodologies currently used to analyze LDL subfractions [35]. In fact, no method is regarded as the golden standard for LDL subfraction analysis or for estimation of LDL particle size [35]. In the present study, we used the Lipophor AS® System to analyze LDL subfractions. This system provides a rapid LDL subclass analysis using high-resolution 3% polyacrylamide gel tubes, determines the amount of cholesterol contained in each of these fractions, and flags results that exceed the “normal” reference range. This method has been validated as an accurate, inexpensive, and easy-to-use technique for visualizing lipoprotein fractions and subfractions [29]. In this context, the Lipoprint® LDL system, which employs a measurement principle similar to the Lipophor AS® System based on polyacrylamide gel lipoprotein disc electrophoresis, is the only FDA-approved test for measuring LDL subfraction cholesterol levels. The calculated values of sd LDL-AUCs × TC using this system were highly correlated with values for sd LDL–cholesterol using a homogeneous assay (r = 0.81) method [29] and were strongly correlated with ultracentrifugation results for sd LDL (r = 0.95) [36], which is regarded as the most robust method for measurements of sd LDL-C. Therefore, potential error is not expected in comparison to other methods, such as the simple precipitation method, which is also highly correlated with ultra-centrifugation for sd LDL (r = 0.88) [25]. Further, this PAGE method can be performed using a commercial kit and does not require expensive instruments.

SGLT-2 inhibitors can reduce hyperglycemia in patients with T2DM by an insulin-independent manner, namely, reducing renal glucose reabsorption. At the same time, this Dönjiclinic of agents decreases body weight mainly due to reduction in visceral or subcutaneous fat mass [11], which are the main production sites of free fatty acid [37,38]. Therefore, under SGLT-2 inhibitor medication, it is theoretically presumed that the liver may decrease TG production by utilizing the plasma glucose and free fatty acid as substrates, resulting in reduction in serum sd LDL levels through reduced production of TG-rich VLDL in the liver.

In this context, the results of our multiple linear regression analysis among all study subjects, which revealed that the independent factors contributing to the reduction in sd LDL-C levels and sd LDL-C/lb LDL-C ratio were mainly change in TG levels as well as changes in LDL-C levels and body weight, are partially consistent with the above-mentioned mechanisms for sd LDL-C production, although we do not have data regarding changes in free fatty acid levels in this study.

On the other hand, it is unclear whether the small reduction in sd LDL levels (−1.28 mg/dL in the present study) would have an overt clinical benefit during long-term observation. In addition, there is no current consensus regarding the target sd LDL levels in patients with hypercholesterolemia and diabetes. In the SATURN trial, which used two intensive statin regimens [39], the final sd LDL level was non-significantly reduced in the rosvastatin 40 mg daily group compared to that in the atorvastatin 80 mg daily group (18.3 ± 12.5 vs. 19.1 ± 12.2 mg/dL; MD, −0.80 mg/dL; 95% CI, −2.30 to 0.70 mg/dL; p = 0.30), and the frequency of the first major adverse cardiovascular event was similar in the two groups (7.5% and 7.1%, respectively).

Some previous studies have reported that SGLT-2 inhibitors are associated with a small increase in HDL-C as well as an increase in LDL-C with concomitant reductions in triglyceride (TG) levels [16,17]. In particular, canagliflozin is associated with an average 8% increase in plasma levels of LDL-C compared with placebo [40], mechanisms of which have not been elucidated.

In contrast with these previous studies using other SGLT-2 inhibitors, the mechanism underlying the significant reduction in LDL-C levels by administration of 50 mg ipragliflozin should be elucidated. First, under treatment with an SGLT-2 inhibitor, LDL-C production is theoretically supposed to decrease through reduced VLDL production, a precursor of LDL, in the liver. In fact, post-hoc subgroup analyses using data from a phase III study of canagliflozin in Japanese patients with T2DM [41] showed that the mean LDL-C level decreased in subgroups with a baseline LDL-C level ≥120 mg/dL that were treated with canagliflozin at doses of 100 mg and 200 mg, indicating that this agent did not increase the risk of LDL-C elevation in the LDL-C ≥120 mg/dL subgroup.

By contrast, it is very difficult to understand the contradictory effects on LDL-C levels observed in this study with those of other studies, such as those using canagliflozin [17,40], since in all of these studies, the mean LDL-C levels of subjects were all under 120 mg/dL. The treatment group in this study had a high frequency of combination therapy with DPP-4 inhibitors, mainly sitagliptin, compared with the treatment groups of previous studies [17,40] (80% vs. 0% and 0%, respectively). Amelioration of glucose toxicity via SGLT2 inhibition might augment the LDL-C-lowering effect of DPP-4 inhibitors associated with a high frequency of statin use in this study.

Table 2

| Variables | β coefficient | Standard error | t value | p value |
|-----------|---------------|---------------|---------|---------|
| (A) Intercept | 1.742 | 6.321 | 0.276 | 0.786 |
| Change in BW (kg) | 1.546 | 0.540 | 2.865 | 0.006 |
| Change in TG (mg/dL) | 0.027 | 0.010 | 2.648 | 0.011 |
| Change in LDL-C (mg/dL) | 0.085 | 0.037 | 2.324 | 0.024 |
| Change in HbA1c (%) | 0.0663 | 1.116 | 0.094 | 0.555 |
| Multiple R-squared (r²) | 0.328 | | | |
| (B) Intercept | 12.90 | 14.80 | 0.871 | 0.388 |
| Change in TG (mg/dL) | 0.084 | 0.024 | 3.492 | 0.001 |
| Change in BW (kg) | 2.902 | 1.263 | 2.297 | 0.026 |
| Change in HbA1c (%) | −0.331 | 2.613 | −0.127 | 0.900 |
| Multiple R-squared (r²) | 0.324 | | | |

(A) Dependent variable: Δsd LDL-C (mg/dL).
(B) Dependent variable: Δsd LDL-C/lb LDL-C ratio (%). Independent variables: sex, age, change in BW, diabetes duration (years), changes in LDL-C, changes in TG, and change in HbA1c (%). Sex: female = 0, male = 1. Sex, age, diabetes duration, and change in HbA1c within the model A, and sex, age, diabetes duration, change in HbA1c and in LDL-C within the model B were not retained, because they were not significant predictors.

BW: body weight, LDL-C: LDL-cholesterol, TG: triglyceride, HbA1c: hemoglobin A1c.
Conflict of interest

Yukihiro Bando has served on advisory boards for Astellas Pharma Inc.

Yukihiro Bando has received speaker honoraria from Astellas Pharma Inc., Eli Lilly Japan K.K., Sanofi K.K., Novo Nordisk Pharma Ltd., Novartis Pharma K.K., MSD K.K. and Takeda Pharmaceutical Company Limited. Other authors have no conflict of interest.

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Appendix. Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.jcte.2016.06.001.

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