



HOKKAIDO UNIVERSITY

Title	Effect of switching from pioglitazone to the sodium glucose co-transporter-2 inhibitor dapagliflozin on body weight and metabolism-related factors in patients with type 2 diabetes mellitus : An open-label, prospective, randomized, parallel-group comparison trial
Author(s)	Cho, Kyu Yong; Nakamura, Akinobu; Omori, Kazuno et al.
Citation	Diabetes, Obesity and Metabolism, 21(3), 710-714 https://doi.org/10.1111/dom.13557
Issue Date	2019-03
Doc URL	https://hdl.handle.net/2115/72905
Rights(URL)	https://creativecommons.org/licenses/by-nc/4.0/
Type	journal article
File Information	Cho_et_al-2019-Diabetes,_Obesity_and_Metabolism.pdf



BRIEF REPORT

Effect of switching from pioglitazone to the sodium glucose co-transporter-2 inhibitor dapagliflozin on body weight and metabolism-related factors in patients with type 2 diabetes mellitus: An open-label, prospective, randomized, parallel-group comparison trial

Kyu Yong Cho MD^{1,2}  | Akinobu Nakamura MD¹  | Kazuno Omori MD¹ | Takahiro Takase MD¹  | Aika Miya MD¹  | Naoki Manda MD³ | Yoshio Kurihara MD⁴ | Shin Aoki MD⁵ | Tatsuya Atsumi MD¹ | Hideaki Miyoshi MD^{1,6}

¹Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

²Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan

³Manda Memorial Hospital, Sapporo, Japan

⁴Kurihara Clinic, Sapporo, Japan

⁵Aoki Clinic, Sapporo, Japan

⁶Division of Diabetes and Obesity, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

Correspondence

Hideaki Miyoshi, MD, PhD, Division of Diabetes and Obesity, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, N15 W7, Kita-ku, Sapporo 060-8638, Japan.
Email: hmiyoshi@med.hokudai.ac.jp

Funding information

There was no financial support for the trial.

The effects of dapagliflozin (DAP) and pioglitazone (PIO) on body weight and glycaemic control were compared in patients with type 2 diabetes mellitus. Seventy-one patients on PIO were either switched to DAP ($n = 36$) at 5 mg per day or continued on PIO ($n = 35$). Primary end-points were superiority of body weight loss and non-inferiority of HbA1c level after 24 weeks with DAP. Body weight decrease was greater with DAP than with PIO (75.3 ± 14.9 to 71.3 ± 15.1 kg vs. 74.7 ± 13.8 to 75.2 ± 13.9 kg; $P < 0.01$). Change in the HbA1c level was comparable ($P = 0.64$). The level of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and urinary albumin : creatinine ratio (ACR) decreased only with DAP (NT-proBNP, $P < 0.01$; ACR, $P = 0.02$), and the change in NT-proBNP correlated negatively with baseline NT-proBNP level ($\rho = -0.68$, $P < 0.01$) and log-converted ACR ($\rho = -0.35$, $P < 0.05$). DAP promotes body weight loss in type 2 diabetes mellitus and may decrease fluid retention, thus reducing the occurrence of cardiovascular events.

KEYWORDS

body weight control, cardiovascular disease, randomized trial, SGLT2 inhibitor, thiazolidinediones, type 2 diabetes

1 | INTRODUCTION

Sodium glucose co-transporter-2 inhibitors (SGLT2is) have been reported to suppress cardiovascular events including heart failure in patients with type 2 diabetes mellitus (T2DM).^{1,2} Similarly, the suppressive effect of pioglitazone (PIO), a thiazolidinedione, on cardiovascular events has been reported.³ However, previous cardiovascular studies have shown a significant increase in hospitalization for heart failure in patients receiving thiazolidinediones,

precluding the use of PIO in patients with severe heart failure.³ A higher prevalence of undiagnosed heart failure among elderly adults with T2DM and higher mortality from heart failure among individuals with diabetes than in those without diabetes has been reported.⁴ There is a risk, therefore, that PIO may be prescribed to patients with undiagnosed heart failure because of the high morbidity of patients with diabetes. Although switching from PIO to SGLT2is appears to be associated with benefits such as reduced body weight gain and fluid retention, to date no reports have

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2018 The Authors. *Diabetes, Obesity and Metabolism* published by John Wiley & Sons Ltd.

evaluated the effects of switching on body weight and glycaemic control.

PIO use has decreased because of an association with increased risk of bladder cancer, as identified from animal studies and a cumulative meta-analysis of observational studies.⁵ Almost all patients currently receiving PIO are therefore good responders in terms of glucose-lowering effects, and are at risk of worsening glycaemic control if switched to other hypoglycaemic agents. To evaluate the superiority of body weight loss and non-inferiority of glycaemic control of SGLT2is compared with PIO, we determined the efficacy of the SGLT2i dapagliflozin (DAP) in patients with T2DM switching from PIO.

2 | METHODS

2.1 | Study design

We conducted a 24-week, open-label, prospective, randomized, parallel-group comparison study at seven sites in Hokkaido, Japan. Screening started in July 2016 and recruitment was completed in February 2017. The trial was registered with the University Hospital Medical Information Network (UMIN) Center (UMIN000022804) before enrolment. The study protocol was approved by the Ethics Review Board of Hokkaido Hospital, and was carried out according to the principles of the Declaration of Helsinki and its amendments. All participants provided written informed consent prior to enrolment.

Participants were assigned randomly to continue taking the Japanese standard dose of PIO (15–30 mg) or to switch to the Japanese standard dose of DAP (5 mg/d), and there were no dose adjustments in principle during the trial. Other anti-T2DM drugs were maintained at a stable dose from enrolment until the end of the treatment period. However, the dose of sulfonylureas and insulin could be reduced if there was a risk of hypoglycaemia with DAP (5 mg/d). Randomization and allocation of participants were performed by a specialized centre independent of the participating sites. Allocation factors included body mass index (BMI) and levels of HbA1c and alanine aminotransferase (ALT).

2.2 | Inclusion and exclusion criteria

The key inclusion criteria were as follows: Japanese patients with T2DM; age, 20–80 years; HbA1c, 6.5%–8.5%; BMI ≥ 23 kg/m²; estimated glomerular filtration rate (eGFR) ≥ 45 mL min⁻¹ 1.73 m⁻²; and treatment with PIO for ≥ 12 weeks before enrolment. Full details of the inclusion and exclusion criteria are provided in Appendix S1 (see the supporting information for this article).

2.3 | Endpoints and assessments

The primary endpoints were superiority of body weight loss and non-inferiority of HbA1c level in the DAP group. Secondary endpoints were change from baseline in abdominal circumference, blood pressure, lipid levels, liver function, heart function and renal function at 24 weeks, and occurrence of adverse effects including hypoglycaemic

events. Data were collected following overnight fasting at baseline and at 24 weeks. The sample size calculation and statistical analysis methods are described in Appendix S2.

TABLE 1 Clinical characteristics of the study cohort

Variable	Dapagliflozin (n = 36)	Pioglitazone (n = 35)	P value
Age, y	63.1 $\pm$ 10.0	63.6 $\pm$ 10.2	0.80
Male sex, n (%)	23 (63.9)	19 (54.3)	0.41
Height, cm	162.5 $\pm$ 9.5	161.6 $\pm$ 8.9	0.68
Body mass index, kg/m ²	28.7 $\pm$ 6.2	28.5 $\pm$ 4.2	0.90
Duration of diabetes, n (%)			0.48
<5 y	5 (13.9)	4 (11.4)	
>5–10 y	8 (22.2)	6 (17.1)	
>10–15 y	11 (30.6)	9 (25.7)	
>15 y	10 (27.8)	16 (45.7)	
Smoking status, n (%)			0.70
Current smoker	8 (22.2)	7 (20.0)	
Former smoker	9 (25.0)	9 (25.7)	
Alcohol drinking status, n (%)	5 (13.9)	2 (5.7)	0.34
Diabetic retinopathy, n (%)	7 (19.4)	13 (37.1)	0.10
Diabetic nephropathy, n (%)	10 (27.8)	16 (45.7)	0.11
Microalbuminuria	8 (22.2)	12 (34.3)	
Macroalbuminuria	2 (5.6)	4 (11.4)	
Atherosclerotic vascular disease, n (%)			
Coronary	5 (13.9)	6 (17.1)	1.00
Cerebrovascular	2 (5.6)	4 (11.4)	0.43
Peripheral	1 (2.8)	3 (8.6)	0.35
Hypertension, n (%)	23 (63.9)	28 (80.0)	0.18
Dyslipidaemia, n (%)	33 (91.7)	30 (85.7)	0.48
Fatty liver, n (%)	7 (19.7)	8 (22.9)	0.72
Treatment for diabetes mellitus			
Oral antidiabetic drug therapy, n (%)			
Dose of pioglitazone 15/30 (mg/day)	30 (83.3) / 6 (16.7)	24 (68.6) / 11 (31.4)	0.15
Biguanide	20 (55.6)	26 (74.3)	0.10
Sulfonylurea	10 (27.8)	9 (25.7)	0.84
Glinide	2 (5.6)	2 (5.7)	1.00
DPP-4 inhibitor	15 (41.7)	22 (62.9)	0.07
α -GI	6 (16.7)	5 (14.3)	0.78
Insulin, n (%)	6 (16.7)	4 (11.4)	0.74
GLP-1 analog, n (%)	3 (8.3)	2 (5.7)	1.00
ACE inhibitor/ARB, n (%)	21 (58.3)	23 (65.7)	0.52
CCB, n (%)	15 (41.7)	20 (57.1)	0.19
Beta-blocker, n (%)	1 (2.8)	4 (11.4)	0.20
Diuretic, n (%)	2 (5.6)	2 (5.7)	1.00
Statin, n (%)	23 (63.9)	27 (77.1)	0.22
Fibrate, n (%)	7 (19.4)	6 (17.1)	0.80
Ezetimibe, n (%)	4 (11.1)	5 (14.3)	0.74

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; α -GI, α -glucosidase inhibitor. Values are mean $\pm$ SD or median (25–75% CI). P value: DAP vs. PIO groups.

3 | RESULTS

3.1 | Participants

Seventy-one patients were screened and randomized to the DAP group ($n = 36$) or PIO group ($n = 35$) (Figure S1). All patients completed the trial. Table 1 presents the baseline characteristics of participants, showing a similar profile between the two groups. In the DAP group, two patients had a decreased sulfonylurea dose and one had decreased insulin units during allocation and follow-up, but these changes were not significant (data not shown). Body weight, abdominal circumference, blood pressure and biochemical analyses at baseline showed no significant differences between the groups (Table 2).

3.2 | Endpoints

Body weight was significantly lower at 24 weeks compared with baseline in the DAP group ($P < 0.01$), and this change was greater in the DAP group than that in the PIO group ($P < 0.01$). The HbA1c level in both groups showed a slight increase (DAP, $P < 0.05$; PIO, $P < 0.05$),

but there was no significant difference between the two groups. The albumin : creatinine ratio (ACR) and level of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) declined only in the DAP group between baseline and 24 weeks (ACR, $P < 0.05$; NT-proBNP, $P < 0.01$), and there was a significant difference between the two groups (ACR, $P < 0.01$; NT-proBNP, $P = 0.02$). Although haematocrit level increased significantly in the DAP group compared with the PIO group ($P < 0.01$), there were no significant differences in change in blood pressure, liver function, renal function or lipid levels from baseline to 24 weeks between the two groups.

The primary endpoints of change in body weight and HbA1c level were unrelated to each other in the DAP group, but showed a significant positive correlation in the PIO group ($\rho = 0.43$, $P < 0.05$) (Figure S2). Change in body weight and HbA1c level had no relationship with other variables. Change in NT-proBNP level from baseline to 24 weeks showed a negative correlation with NT-proBNP level at baseline in both groups, and the correlation was stronger in the DAP group ($\rho = -0.68$, $P < 0.01$) (Figure S3A). Similarly, change in NT-proBNP level from baseline to 24 weeks showed a negative correlation with log-converted ACR level at baseline in the DAP group

TABLE 2 Comparison of variables in the dapagliflozin and pioglitazone groups

Variable	Dapagliflozin		Pioglitazone		P value
	Baseline	After 24 weeks	Baseline	After 24 weeks	
Body weight (kg)	75.3 $\pm$ 14.9	71.3 $\pm$ 15.1**	74.7 $\pm$ 13.8	75.2 $\pm$ 13.9	<0.01
Abdominal circumference (cm)	96.1 $\pm$ 9.6	93.0 $\pm$ 10.1**	98.5 $\pm$ 9.4	98.3 $\pm$ 10.8	<0.01
SBP (mm Hg)	129.2 $\pm$ 11.4	125.8 $\pm$ 14.0	131.1 $\pm$ 11.4	132.3 $\pm$ 13.5	0.31
DBP (mm Hg)	78.7 $\pm$ 9.9	75.1 $\pm$ 10.6	74.5 $\pm$ 13.1	75.2 $\pm$ 11.4	0.13
Biochemical variables					
FPG (mmol/L)	7.2 $\pm$ 1.2	7.3 $\pm$ 1.3	7.1 $\pm$ 1.1	7.4 $\pm$ 1.4	0.52
HbA1c (%)	6.9 $\pm$ 0.6	7.0 $\pm$ 0.7 *	6.9 $\pm$ 0.6	7.1 $\pm$ 0.8*	0.64
Insulin (μ U/mL) ^a	5.8 (4.0–6.6)	5.6 (4.0–6.5)	5.0 (3.4–6.5)	5.6 (4.2–6.5)*	0.02
HOMA-IR ^a	1.7 (1.3–2.2)	1.7(1.4–2.5)	1.4 (1.1–2.1)	1.7 (1.2–2.8)	0.09
C-peptide (ng/mL) ^b	1.4 (1.0–1.7)	1.4 (0.9–2.0)	1.8 (1.0–2.1)	2.3 (1.4–2.8)**	0.02
Total cholesterol (mg/dL)	179.0 (154.3–201.3)	182.0 (166.3–198.0)	167.0 (152.0–196.0)	175.0 (158.0–191.0)	0.81
LDL-cholesterol (mg/dL)	93.0 (82.3–104.0)	97.0 (80.0–109.8)	91.0 (79.0–111.0)	94.0 (81.0–106.0)	0.30
HDL-cholesterol (mg/dL)	56.5 (49.0–68.2)	54.5 (46.3–70.3)	54.0 (47.0–65.0)	55.0 (48.0–64.0)	0.42
Triglyceride (mg/dL)	107.0 (59.0–150.0)	104.5 (80.3–151.0)	91.0 (75.8–132.0)	103.0 (80.0–164.0)	0.56
Haemoglobin (g/L)	141.5 $\pm$ 9.8	149.8 $\pm$ 14.4**	135.9 $\pm$ 14.1	139.0 $\pm$ 11.0	0.11
Haematocrit (%)	42.9 $\pm$ 2.8	45.0 $\pm$ 4.3**	41.8 $\pm$ 3.6	41.7 $\pm$ 3.6	<0.01
BUN (mg/dL)	16.4 $\pm$ 4.1	18.0 $\pm$ 4.2**	16.2 $\pm$ 4.1	16.5 $\pm$ 5.4	0.02
Creatinine (mg/dL)	0.8 $\pm$ 0.2	0.8 $\pm$ 0.2	0.8 $\pm$ 0.2	0.8 $\pm$ 0.2	0.91
eGFR (mL min ⁻¹ 1.73 m ⁻²)	72.4 $\pm$ 19.6	70.8 $\pm$ 17.6	67.1 $\pm$ 16.8	65.8 $\pm$ 15.6	0.43
UA (mg/dL)	5.3 $\pm$ 1.6	5.1 $\pm$ 1.5	5.7 $\pm$ 1.1	5.6 $\pm$ 1.0	0.60
AST (IU/L)	23.4 $\pm$ 11.5	21.7 $\pm$ 10.7*	23.5 $\pm$ 6.8	23.2 $\pm$ 6.4	0.23
ALT (IU/L)	22.7 $\pm$ 13.1	21.4 $\pm$ 11.6	23.5 $\pm$ 12.1	22.1 $\pm$ 10.4	0.98
γ -GTP (IU/L)	21.5 (16.2–35.0)	21.0 (18.3–27.8)	20.0 (17.0–26.0)	20.0 (16.0–31.0)	0.48
NT-proBNP (pg/mL)	36.5 (21.3–82.5)	22.0 (12.3–49.8)**	35.0 (19.0–66.0)	37.5 (15.5–61.0)	0.02
ACR (mg/g)	22.1 (8.3–32.9)	10.1 (7.0–32.7)*	26.5 (10.6–46.3)	36.9 (11.3–120.0)	<0.01

Abbreviations: ACR, albumin : creatinine ratio; DBP, diastolic blood pressure; FPG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SBP, systolic blood pressure; BUN, blood urea nitrogen; UA, uric acid; ALT, alanine transaminase; γ -GTP, γ -glutamyl transpeptidase.

Values are mean $\pm$ SD or median (25–75% CI).

^a Data from 58 patients (dapagliflozin, $n = 28$; pioglitazone, $n = 30$).

^b Data from 19 patients (dapagliflozin, $n = 8$; pioglitazone, $n = 11$).

P value: mean changes between baseline and the end of the study (Welch's *t* test or Mann–Whitney U test). * $P < 0.05$ and ** $P < 0.01$ between baseline and end of the study (paired-sample *t* tests or Wilcoxon signed rank test).

($p = -0.36$, $P < 0.05$), but no relationship was observed in the PIO group (Figure S3B). Finally, no correlation was observed between baseline NT-proBNP level and baseline log-converted ACR level ($p = 0.14$, $P = 0.16$).

3.3 | Safety

Few adverse events were reported in either the DAP group or the PIO group in the 24-week study period (Table S1). Those adverse events that did occur were mild, and were resolved with appropriate observation and administration of antibiotics. No patients discontinued from the trial or reported a recurrent infection, severe hypoglycaemia, dehydration, ketoacidosis or a cardiovascular event.

4 | DISCUSSION

In the present study, superiority in body weight loss and non-inferiority in HbA1c level was shown for DAP compared with PIO after 12 weeks of treatment. Although mean HbA1c increased slightly in both groups during the study, glycaemic control was comparable between the groups. In the DAP group, body weight was significantly reduced, regardless of the change in HbA1c level. The clear reduction in body weight upon switching from PIO to DAP which was observed could be explained by the effect of PIO on fluid retention in addition to the reduction in body fat mass. It has been suggested that SGLT2is may suppress cardiovascular events by reducing excess fluid. The improvement in rate of subclinical heart failure has been shown to be closely related to the positive effect of SGLT2is on cardiovascular event and death in recent large-scale studies.^{2,6} T2DM is an important risk factor for the development of chronic heart failure (CHF), and the combination of T2DM and CHF is associated with high mortality for heart failure.^{4,7} Additional analyses of the ADVANCE study showed that higher NT-proBNP level was associated with increased onset and progression of heart failure in patients with T2DM.⁸ In the present study, mean NT-proBNP level was not high because patients with clinically relevant CHF were excluded from the study population. However, a certain level of ventricular overload has been reported when the NT-proBNP level reaches 55 pg/mL.⁹ Some patients [DAP group: 10 (27.8%); PIO group: 10 (28.5%)] had baseline NT-proBNP values of >55 pg/mL, and the improvement in NT-proBNP level in the DAP group was particularly significant in this population. ACR declined only in the DAP group; higher baseline ACR was associated with greater decline in NT-proBNP level. Recent clinical trials have shown that SGLT2is exert strong protective and enhancing effects on renal function compared with other anti-T2DM medications.^{2,10} Improvement in renal function following SGLT2i treatment may indirectly result in lowering of the cardiovascular risk associated with renal dysfunction (cardiorenal syndrome) in patients with T2DM. Another recent study showed that ACR may represent a useful biomarker to identify patients with diabetes at increased cardiovascular risk from a diffuse cardiac fibrotic process.¹¹ However, NT-proBNP has been shown to be affected by renal function,¹² although baseline NT-proBNP values had no correlation with the baseline ACR in the present trial. The significant correlation between change in

NT-proBNP and baseline ACR may therefore reflect the therapeutic advantage of DAP administration by reducing excess fluid or sodium levels in patients with nephropathy.

Our study had two important limitations. First, this randomized controlled trial had an open-label design, which might have contributed to bias. Second, the study was conducted only with Japanese patients. Whether our results can be generalized to non-Japanese patients remains unknown.¹³ Nevertheless, the beneficial effects of SGLT2is on the risk of cardiovascular events have been shown to be consistent between Asian patients and a general patient population with T2DM.¹⁴

Our findings show that a significant reduction in body weight, regardless of the effect on glycaemic control, can be obtained by switching from PIO to SGLT2is. Moreover, this switching of medication may have other beneficial effects on cardiac and renal function.

ACKNOWLEDGMENTS

The authors thank the participants, their families, and all the investigators involved in this study. We also thank Arshad Makhdom, PhD, and Clare Cox, PhD, from the Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

CONFLICT OF INTEREST

Nakamura A, Manda N, Kurihara Y, Atsumi T, and Miyoshi H have received honoraria for lectures and received research funding from some organizations as described below. The other authors declare no conflict of interest. Nakamura A. has received research funding from Mitsubishi Tanabe Pharma Co., Ono Pharmaceutical Co., Ltd. Manda N. has received honoraria for lectures from Ono Pharmaceutical Co., Ltd. Kurihara Y. has received honoraria for lectures from Astellas Pharma Inc., AstraZeneca, Mitsubishi Tanabe Pharma Co., Ltd., MSD, Ono Pharmaceutical Co., Ltd., Sanofi, Shionogi & Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Co., Ltd. Atsumi T. has received honoraria for lectures from Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Pfizer Inc., AbbVie Inc., Eisai Co. Ltd., Daiichi Sankyo Co. Ltd., Bristol-Myers Squibb Co., UCB Japan Co. Ltd., Eli Lilly Japan K.K., and has received research funding from Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co. Ltd., Otsuka Pharmaceutical Co., Ltd., Pfizer Inc., and Alexion Inc. Miyoshi H. has received honoraria for lectures from Astellas Pharma Inc., AstraZeneca, Daiinippon Pharma Co., Eli Lilly, Kissei, Mitsubishi Tanabe Pharma Co., MSD, Novartis Pharma, Novo Nordisk Pharma, Takeda Pharmaceutical Co., Ltd., Kowa Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., and Sanofi; and has received research funding from Astellas Pharma Inc., AstraZeneca, Daiichi Sankyo, Daiinippon Pharma Co., Eli Lilly, Mitsubishi Tanabe Pharma Co., MSD, Novo Nordisk Pharma, Sanofi, Takeda Pharmaceutical Co., Ltd., Kowa Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., and Taisho Toyama Pharmaceutical Co., Ltd.

ORCID

Kyu Yong Cho  <https://orcid.org/0000-0002-3131-0832>

Akinobu Nakamura  <https://orcid.org/0000-0002-8192-0006>

Takahiro Takase  <https://orcid.org/0000-0001-6089-2395>

Aika Miya  <https://orcid.org/0000-0002-3313-6946>

REFERENCES

1. EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117-2128.
2. CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644-657.
3. PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (PROspective pioglitAzone clinical trial in macroVascular events): a randomized controlled trial. *Lancet*. 2005;366:1279-1289.
4. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC Jr. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care*. 2004;27:699-703.
5. Tang H, Shi W, Fu S, et al. Pioglitazone and bladder cancer risk: a systematic review and meta-analysis. *Cancer Med*. 2018;7:1070-1080.
6. EMPA-REG OUTCOME[®] trial investigators. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME[®] trial. *Eur Heart J*. 2018;39:363-370.
7. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care*. 2004;27:1879-1884.
8. ADVANCE Collaborative Group. Cardiac stress and inflammatory markers as predictors of heart failure in patients with type 2 diabetes: the ADVANCE trial. *Diabetes Care*. 2017;40:1203-1209.
9. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the Management of Heart Failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2013;62:e147-e239.
10. EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323-334.
11. Swoboda PP, McDiarmid AK, Erhayiem B, et al. Diabetes mellitus, microalbuminuria, and subclinical cardiac disease: identification and monitoring of individuals at risk of heart failure. *J Am Heart Assoc*. 2017;6:pii-e005539.
12. Farnsworth CW, Bailey AL, Jaffe AS, Scott MG. Diagnostic concordance between NT-proBNP and BNP for suspected heart failure. *Clin Biochem*. 2018;59:50-55.
13. Japan Diabetes Complication Study Group. Obesity and type 2 diabetes in Japanese patients. *Lancet*. 2003;361:85.
14. EMPA-REG OUTCOME[®] Investigators. Empagliflozin and cardiovascular outcomes in asian patients with type 2 diabetes and established cardiovascular disease- results from EMPA-REG OUTCOME[®]. *Circ J*. 2017;81:227-234.

SUPPORTING INFORMATION

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

How to cite this article: Cho KY, Nakamura A, Omori K, et al. Effect of switching from pioglitazone to the sodium glucose co-transporter-2 inhibitor dapagliflozin on body weight and metabolism-related factors in patients with type 2 diabetes mellitus: An open-label, prospective, randomized, parallel-group comparison trial. *Diabetes Obes Metab*. 2019;21:710-714. <https://doi.org/10.1111/dom.13557>