



Safety and efficacy of empagliflozin in elderly Japanese patients with type 2 diabetes mellitus: A post hoc analysis of data from the SACRA study

Kenta Okada MD, PhD¹ | Satoshi Hoshide MD, PhD²  | Mitsutoshi Kato MD, PhD³ | Hiroshi Kanegae BSc² | Shun Ishibashi MD, PhD¹ | Kazuomi Kario MD, PhD² 

¹Division of Endocrinology and Metabolism, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

²Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

³Kato Clinic of Internal Medicine, Tokyo, Japan

Correspondence

Kazuomi Kario, Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke, Tochigi, Japan.
Email: kkario@jichi.ac.jp

Funding information

Eli Lilly and Company Diabetes Alliance; Boehringer Ingelheim

Abstract

Elderly diabetic patients are likely to have uncontrolled nocturnal hypertension, which confers higher risks of cardiovascular events and heart failure. To investigate the efficacy and safety of empagliflozin in elderly patients with type 2 diabetes (T2DM), a sub-analysis was performed of data from the SGLT2 inhibitor and Angiotensin receptor blocker Combination theRapy in pAtients with diabetes and uncontrolled nocturnal hypertension (SACRA) study, a multi-center, double-blind, randomized, parallel study of T2DM patients who were treated with empagliflozin for 12 weeks. In the present analysis, we compared efficacy and safety outcomes in participants aged <75 and ≥75 years. At baseline, 44 participants were ≥75 years and 87 were <75 years. Nighttime ambulatory systolic blood pressure (SBP) decreased by 4.2 mm Hg in the ≥75-year-old group and by 7.9 mm Hg in the <75-year-old group ($p = .884$ for the between-age group difference in the change between baseline and week 12) [primary endpoint]. Empagliflozin, but not placebo, significantly reduced mean 24-h SBP (−8.7 mm Hg in ≥75-year-olds vs. −11.0 mm Hg in <75-year-olds) and daytime SBP (−10.8 mm Hg in ≥75-year-olds vs. −12.3 mm Hg in <75-year-olds) between baseline and week 12, with no significant differences between the groups. In addition, there were significant reductions in glycated hemoglobin, body weight, and uric acid during 12 weeks of empagliflozin treatment in the two age groups. The incidences of hypoglycemic episodes, hypotension, and metabolic adverse events were similar in the two groups. Thus, empagliflozin was effective and well tolerated in elderly diabetic patients with uncontrolled nocturnal hypertension when administered for 12 weeks.

1 | INTRODUCTION

More than 13.8% of the Japanese population is aged ≥75 years and many patients with type 2 diabetes (T2DM) are of advanced age.¹ Elderly adults have specific health problems that vary widely among individuals, and elderly diabetic patients exhibit substantial loss of

organ function and medical heterogeneity.^{2,3} In addition, elderly adults are prone to cognitive impairment, depression, frailty, and adverse events (AEs) resulting from polypharmacy that can further complicate the management of T2DM.^{4–8} Finally, elderly diabetic patients generally have higher prevalences of complications than younger patients and are more likely to require emergency

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2020 The Authors. *The Journal of Clinical Hypertension* published by Wiley Periodicals LLC

treatment for hypoglycemic events.⁴ However, there is little strong clinical evidence regarding the use of medication in elderly patients, especially in those with uncontrolled nocturnal hypertension who were undergoing stable antihypertensive therapy.

The risks of cardiovascular disease (CVD) and mortality are particularly high in T2DM patients with hypertension.^{9–11} Moreover, the incidences of CVD and mortality are particularly high in T2DM patients with nocturnal hypertension.^{9,12,13} In patients at high risk of CVD (excluding those with diabetes mellitus and those who had previously experienced a stroke), SPRINT (the Systolic Blood Pressure Intervention Trial) showed that intensive therapy of clinic systolic blood pressure (SBP) (to maintain SBP at <120 mm Hg) significantly reduced the incidences of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or CVD death versus standard therapy for clinic SBP (to maintain SBP at <140 mm Hg),¹⁴ which implies that a lower SBP target may be preferable to the standard target for CVD prevention in these patients. However, good blood pressure (BP) control, including nighttime BP, is difficult to achieve in patients with T2DM and nocturnal hypertension.

In the recent cardiovascular outcome trials, sodium-glucose cotransporter 2 (SGLT2) inhibitors significantly reduced cardiovascular and all-cause mortality, heart failure-related hospitalization, and the progression of diabetic nephropathy.^{15,16} However, scientific evidence for their efficacy with respect to BP, including nighttime BP, and the safety of SGLT2 inhibitors in elderly diabetic patients is scarce. In the SGLT2 inhibitor and Angiotensin receptor blocker (ARB) Combination theRapy in pAtients with diabetes and uncontrolled nocturnal hypertension (SACRA) study, the use of empagliflozin, an SGLT2 inhibitor, was studied in patients with T2DM and uncontrolled nocturnal hypertension in a randomized, placebo-controlled clinical trial.¹⁷ Empagliflozin (10 mg once daily) reduced both nighttime ambulatory BP and a variety of other BP parameters, including ambulatory, home, and clinic BP, as well as body weight (BW), glycated hemoglobin (HbA1c), and natriuretic peptide concentrations, in diabetic patients who were using ARBs but had uncontrolled nocturnal hypertension. Therefore, the use of SGLT2 inhibitors by diabetic patients with nocturnal hypertension could help reduce their risks of heart failure and cardiovascular mortality.

Here, we report the results of a pre-specified exploratory analysis of the short-term effects of empagliflozin administration on a range of efficacy- and AE-related end points in patients with diabetes and uncontrolled nocturnal hypertension of <75 and ≥75 years of age.

2 | METHODS

2.1 | Study design and participants

The SACRA study (NCT03050229) design, patient selection criteria, and methods have been described in detail in a previous interim report.¹⁷ Briefly, it was a placebo-controlled, double-blind, randomized, two-arm parallel group study that was undertaken across multiple

centers in Japan. Adult patients with T2DM (HbA1c 6%–10%), seated clinic SBP 130–159 mm Hg or diastolic BP (DBP) 80–99 mm Hg, and uncontrolled nocturnal hypertension (SBP ≥ 115 mm Hg at 2, 3, and 4 AM during sleep 5 days prior to randomization, measured using home BP monitoring [HBPM]; HEM-7080-IC; Omron Healthcare Co., Ltd.), who were undergoing stable antihypertensive therapy, including with ARBs, were randomized to 12 weeks' treatment with empagliflozin (10 mg once daily) or placebo.

24-h ambulatory BP monitoring (ABPM) was performed at baseline and after 12 weeks, using methods described previously.¹⁸ ABPM was performed with a validated device (TM2431; A&D Co.). BP was measured every 30 min throughout the day. 24-h BP was defined as the average of all readings over a 24-h period. Nighttime BP was calculated as the average of BP values recorded over the period from when the patient went to bed until they got up; values over the rest of the day were used to calculate daytime BP. BP was measured in the clinic at baseline and after 4, 8, and 12 weeks of treatment; and morning home BP was determined at home over the 5 days prior to each visit, using a validated morning device (HEM-7080-IC; Omron Healthcare Co., Ltd.).

The primary efficacy end point was the change from baseline in nighttime ambulatory BP. The key secondary end points were the changes in mean 24-h SBP, DBP, and daytime BP over 12 weeks. The other secondary efficacy end points were the changes between baseline and week 12 in morning home BP, clinic BP, HbA1c, and BW. The other end points were the serum low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol concentrations; the serum amino-terminal pro-B-type natriuretic peptide (NT-proBNP), atrial natriuretic peptide (ANP), and magnesium concentrations; estimated glomerular filtration rate (eGFR); the urinary albumin: creatinine ratio (UACR); and other laboratory findings. The safety of the intervention was also assessed using the laboratory findings and the incidences of AEs.

The study protocol was approved by the ethics committee of Jichi Medical University School of Medicine (B15-128, 28 September 2016). The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Harmonization Tripartite Guidelines for Good Clinical Practice. All the patients provided their written informed consent before enrollment in the study.

2.2 | Statistical analysis

We conducted a post hoc comparison of data from participants who were ≥75 and <75 years old. The analyses of efficacy with respect to BP values were conducted on the full dataset (FAS). Mixed-effects model-repeated measures (MMRM) analysis was used to compare the changes in nighttime BP, daytime BP, mean 24-h BP, morning home BP, clinic BP, HbA1c, BW, and laboratory findings during the 12-week study period between the groups. The MMRM analysis included the randomized study group, time point (0, 4, 8, and 12 weeks), and the interaction between the study group and time point as fixed effects; and age and sex as covariates. The

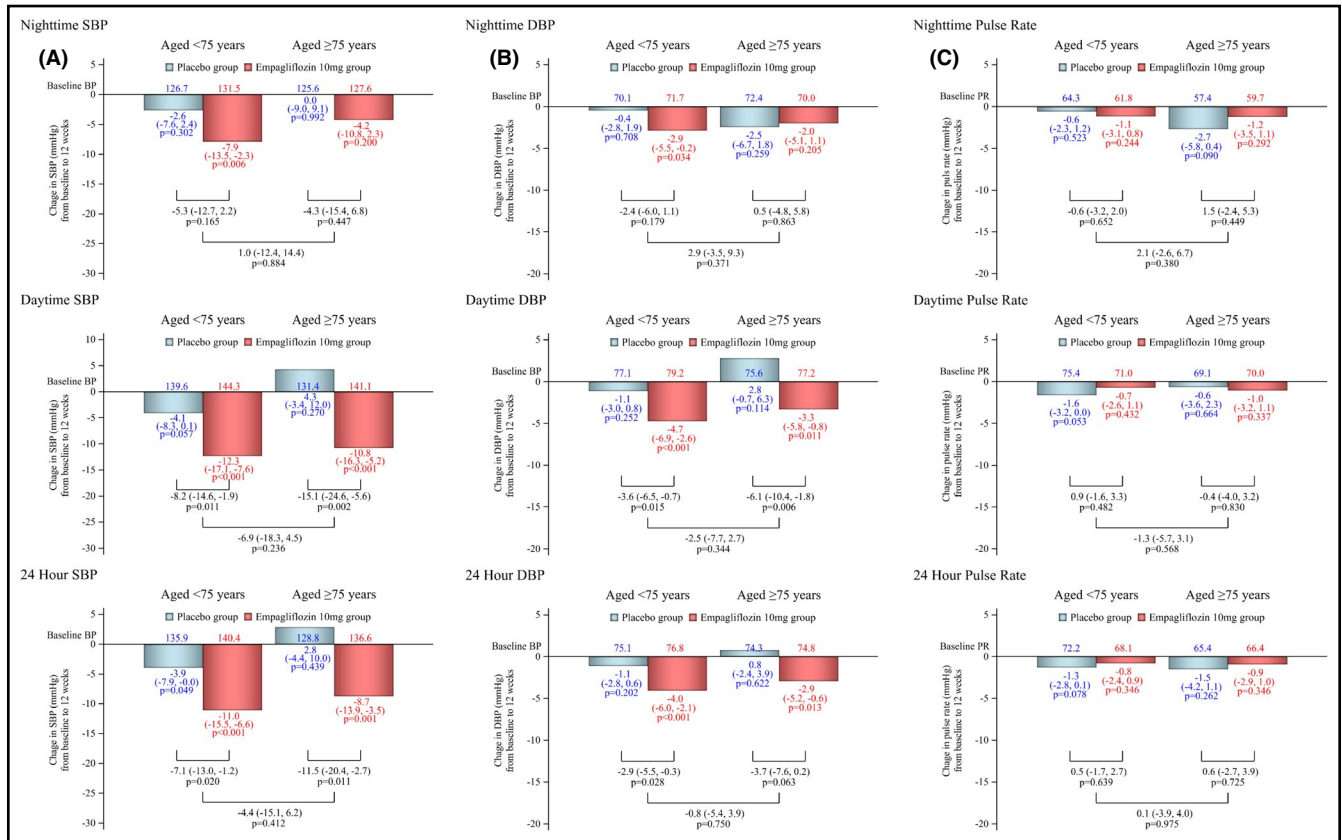


FIGURE 1 Changes from baseline in nighttime, daytime, and 24-h systolic (SBP) (A), diastolic (DBP) (B) blood pressure, and pulse rate (C). Bars and values represent the changes (means and 95% CIs) from baseline, which were compared using mixed-effects models with repeated measures, adjusted for age and sex. The *p*-values quoted are for comparisons of the changes from baseline, and the between-group and between-age group differences

incidence of AEs was determined using the safety analysis dataset. Two-sided tests were used, and $p < .05$ was considered to represent statistical significance. Inter-group comparisons were made using Student's *t* test for continuous data and Pearson's chi-square test or Fisher's exact test for dichotomous data. Data were analyzed using SAS version 9.4 (SAS Institute) at the Jichi Medical University Center of Global Home and Ambulatory BP Analysis (GAP).

3 | RESULTS

3.1 | Baseline characteristics of the participants

The baseline characteristics of the participants are shown in Table 1. A total of 131 participants were allocated to the <75-year-old ($n = 87$) and ≥ 75 -year-old ($n = 44$) groups. There were significant differences between the groups with respect to BW (67.8 ± 14.1 vs. 59.5 ± 7.4 kg, $p < .001$), HbA1c (6.7 ± 0.8 vs. $6.4 \pm 0.6\%$, $p = .015$), serum triglycerides (median; 107 vs. 90 mg/dl, $p = .027$), serum NT-pro BNP (median; 50 vs. 90 pg/dl, $p < .001$), serum ANP (median; 31 vs. 38 pg/dl, $p = .001$), UACR (median; 24.5 vs. 15.1 pg/dl, $p = .037$), and eGFR (72.4 ± 16.4 vs. 62.9 ± 11.6 ml/min/1.73 m², $p < .001$). No other significant differences, including the prevalences of concomitant treatment with

antihypertensive or antidiabetic drugs, were identified between the two groups. There were also no significant differences between each group and the equivalent placebo group (Table S1).

3.2 | Blood pressure measurements

Significant reductions in 24-h BP and daytime BP at 12 weeks from baseline were observed in both the <75 and ≥ 75 years groups (24-h SBP: 11.0 mm Hg vs. 8.7 mm Hg, 24-h DBP: 4.0 mm Hg vs. 2.9 mm Hg, daytime SBP: 12.3 mm Hg vs. 10.8 mm Hg, daytime DBP: 4.7 mm Hg vs. 3.3 mm Hg, all $p < .05$) (Figure 1A,B and Table 2), although nighttime SBP and DBP were not reduced by empagliflozin in either group [primary endpoint]. The pulse rates during each ABPM measurement were similar over 12 weeks, with no significant differences between the groups (Figure 1C).

The differences from baseline to week 12 in the placebo-subtracted 24-h SBP reduction were similar between the groups (<75 years: 7.1 mm Hg, ≥ 75 years: 11.5 mm Hg, $p = .412$) (Figure 1A and Table 2). There were also no significant differences between baseline and week 12 in nighttime BP, daytime BP, or the 24-h DBP placebo-subtracted reduction between the groups (Figure 1A,B and Table 2).

TABLE 1 Clinical characteristics of the participants who were ≥ 75 or < 75 years of age

Variables	Aged < 75 years	Aged ≥ 75 years	p-value
n	87	44	
Age, years	66.0 \pm 7.0	78.4 \pm 3.1	<.001
Males, %	55.2	47.7	.462
Body weight, kg	67.8 \pm 14.1	59.5 \pm 7.4	<.001
BMI, kg/m ²	26.4 \pm 4.8	25.2 \pm 2.9	.116
Diabetes duration, years	10.4 \pm 8.6	9.5 \pm 6.7	.584
HbA1c, %	6.7 \pm 0.8	6.4 \pm 0.6	.015
Medical history, %			
Dyslipidemia	60.9	63.6	.850
Hyperuricemia	11.5	15.9	.583
Cerebrovascular disease	10.3	4.5	.333
Cardiac disease	13.8	22.7	.221
LDL cholesterol, mg/dl	110.6 \pm 27.5	100.7 \pm 27.0	.052
HDL cholesterol, mg/dl	57.6 \pm 18.1	53.8 \pm 13.7	.177
Triglycerides, mg/dl	107 (82, 158)	90 (69, 120)	.027
NT-pro BNP, pg/ml	50 (28, 72)	90 (60, 186)	<.001
ANP, pg/ml	31 (20, 41)	38 (29, 54)	.001
Uric acid, mg/dl	5.4 \pm 1.6	5.5 \pm 1.5	.519
UACR, mg/g·Cr	24.5 (11.7, 87.9)	15.1 (7.5, 33.9)	.037
eGFR, ml/min/1.73m ²	72.4 \pm 16.4	62.9 \pm 11.6	<.001
Creatinine, mg/dl	99.9 \pm 64.5	85.9 \pm 58.4	.214
Antihypertensive therapy, %			
ARB	100.0	100.0	–
Calcium channel blockers	64.4	75.0	.241
Diuretics	24.1	34.1	.300
α -blocker	10.3	2.3	.163
β -blocker	11.5	20.5	.194
Other	3.5	4.6	1.000
Antidiabetic therapy, %			
DPP-4 inhibitor	57.5	47.7	.354
Glinide	3.5	9.1	.224
GLP-1 receptor agonist	1.2	0.0	1.000
Metformin	31.0	25.0	.544
Thiazolidinedione	8.1	0.0	.095
α -glucosidase inhibitor	6.9	6.8	1.000

Note: Values are mean \pm SD, median (interquartile range), or the percentage of participants.

Abbreviations: ACE, angiotensin-converting enzyme; ANP, atrial natriuretic peptide; BMI, body mass index; Cr, creatinine; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-pro BNP, amino-terminal pro-B-type natriuretic peptide; UACR, urinary albumin: creatinine ratio.

In addition, there were larger reductions in morning home SBP from baseline to week 12 in participants taking either empagliflozin or placebo (Table 2), although the differences in placebo-subtracted morning home SBP at week 12 were similar, regardless of age. In contrast, there was a larger reduction in clinic SBP between baseline and week 12 in participants taking empagliflozin (Table 2), and there were significant differences in the placebo-subtracted clinic SBP and DBP reduction between baseline and week 12 between the age

groups (clinic SBP: -12.6 mm Hg, $p < .05$, clinic DBP: -10.2 mm Hg, $p < .01$).

3.3 | HbA1c, body weight, and laboratory findings

HbA1c was reduced by empagliflozin to a similar extent in the < 75 -year-olds and the ≥ 75 -year-olds (-0.24% vs. -0.28% at week

TABLE 2 Values of the parameters measured in participants who were ≥ 75 or < 75 years of age during the treatment period

	Aged < 75 years		Aged ≥ 75 years	
	Placebo (n = 49)	Empagliflozin (n = 38)	Placebo (n = 14)	Empagliflozin (n = 30)
Nighttime SBP, mm Hg				
Baseline	126.7 \pm 2.9	131.5 \pm 3.3	125.6 \pm 5.5	127.6 \pm 4.0
Week 12	124.1 \pm 2.9	123.6 \pm 3.3	125.6 \pm 5.5	123.4 \pm 4.1
Change after 12 weeks	-2.6 \pm 2.5	-7.9 \pm 2.8 ^{††}	0.0 \pm 4.5	-4.2 \pm 5.6
Between-group difference in change after 12 weeks		-5.3 \pm 3.8		-4.3 \pm 5.6
Nighttime DBP, mm Hg				
Baseline	70.1 \pm 1.4	71.7 \pm 1.6	72.4 \pm 2.7	70.0 \pm 1.9
Week 12	69.6 \pm 1.4	68.8 \pm 1.6	69.9 \pm 2.7	67.9 \pm 2.0
Change after 12 weeks	-0.4 \pm 1.2	-2.9 \pm 1.3	-2.5 \pm 2.2	-2.0 \pm 1.6
Between-group difference in change after 12 weeks		-2.4 \pm 1.8		0.5 \pm 2.7
Nighttime PR, beat/min				
Baseline	64.3 \pm 1.2	61.8 \pm 1.4	57.4 \pm 2.3	59.7 \pm 1.7
Week 12	63.7 \pm 1.2	60.6 \pm 1.4	54.8 \pm 2.3	58.5 \pm 1.8
Change after 12 weeks	-0.6 \pm 0.9	-1.1 \pm 1.0	-2.7 \pm 1.6	-1.2 \pm 1.1
Between-group difference in change after 12 weeks		-0.6 \pm 1.3		1.5 \pm 1.9
Daytime SBP, mm Hg				
Baseline	139.6 \pm 2.3	144.3 \pm 2.7	131.4 \pm 4.5	141.1 \pm 3.2
Week 12	135.5 \pm 2.3	132.0 \pm 2.7	135.7 \pm 4.5	130.4 \pm 3.4
Change after 12 weeks	-4.1 \pm 2.1	-12.3 \pm 2.4 ^{††}	4.3 \pm 3.9	-10.8 \pm 2.8 ^{††}
Between-group difference in change after 12 weeks		-8.2 \pm 3.2 [*]		-15.1 \pm 4.8 ^{**}
Daytime DBP, mm Hg				
Baseline	77.1 \pm 1.1	79.2 \pm 1.3	75.6 \pm 2.1	77.2 \pm 1.6
Week 12	76.0 \pm 1.1	74.4 \pm 1.3	78.4 \pm 2.1	73.9 \pm 1.6
Change after 12 weeks	-1.1 \pm 1.0	-4.7 \pm 1.1 ^{††}	2.8 \pm 1.8	-3.3 \pm 1.3 [†]
Between-group difference in change after 12 weeks		-3.6 \pm 1.5 [*]		-6.1 \pm 2.2 ^{**}
Daytime PR, beat/min				
Baseline	75.4 \pm 1.2	71.0 \pm 1.4	69.1 \pm 2.3	70.0 \pm 1.7
Week 12	73.8 \pm 1.2	70.3 \pm 1.4	68.4 \pm 2.3	68.9 \pm 1.7
Change after 12 weeks	-1.6 \pm 0.8	-0.7 \pm 0.9	-0.6 \pm 1.5	-1.0 \pm 1.1
Between-group difference in change after 12 weeks		0.9 \pm 1.2		-0.4 \pm 1.8
24 h SBP, mm Hg				
Baseline	135.9 \pm 2.4	140.4 \pm 2.7	128.8 \pm 4.5	136.6 \pm 3.3
Week 12	131.9 \pm 2.4	129.4 \pm 2.7	131.6 \pm 4.5	127.8 \pm 3.4
Change after 12 weeks	-3.9 \pm 2.0	-11.0 \pm 2.2 ^{††}	2.8 \pm 3.6	-8.7 \pm 2.6 ^{††}
Between-group difference in change after 12 weeks		-7.1 \pm 3.0 [*]		-11.5 \pm 4.5 [*]
24 h DBP, mm Hg				
Baseline	75.1 \pm 1.1	76.8 \pm 1.3	74.3 \pm 2.1	74.8 \pm 1.5
Week 12	74.0 \pm 1.1	72.7 \pm 1.3	75.1 \pm 2.1	71.9 \pm 1.6
Change after 12 weeks	-1.1 \pm 0.9	-4.0 \pm 1.0 ^{††}	0.8 \pm 1.6	-2.9 \pm 1.2 [†]

(Continues)

Table 2 (Continued)

	Aged <75 years		Aged ≥75 years	
	Placebo (n = 49)	Empagliflozin (n = 38)	Placebo (n = 14)	Empagliflozin (n = 30)
Between-group difference in change after 12 weeks		-2.9 ± 1.3 [*]		-3.7 ± 2.0
24 h PR, beat/min				
Baseline	72.2 ± 1.2	68.1 ± 1.3	65.4 ± 2.2	66.4 ± 1.6
Week 12	70.8 ± 1.2	67.4 ± 1.3	63.8 ± 2.2	65.5 ± 1.7
Change after 12 weeks	-1.3 ± 0.7	-0.8 ± 0.8	-1.5 ± 1.3	-0.9 ± 1.0
Between-group difference in change after 12 weeks		0.5 ± 1.1		0.6 ± 1.6
Morning home SBP, mm Hg				
Baseline	140.0 ± 1.9	142.5 ± 2.2	139.9 ± 3.9	135.4 ± 2.7
Week 12	133.6 ± 1.9	127.6 ± 2.2	139.2 ± 3.9	125.4 ± 2.9
Change after 12 weeks	-6.3 ± 1.4 ^{††}	-14.9 ± 1.7 ^{††}	-0.7 ± 2.9	-10.0 ± 2.0 ^{††}
Between-group difference in change after 12 weeks		-8.6 ± 1.7 ^{**}		-9.3 ± 3.5 ^{**}
Morning home DBP, mm Hg				
Baseline	74.2 ± 1.2	78.1 ± 1.4	77.2 ± 2.5	72.3 ± 1.7
Week 12	72.7 ± 1.2	72.3 ± 1.4	77.0 ± 2.5	69.2 ± 1.8
Change after 12 weeks	-1.5 ± 0.7 [†]	-5.9 ± 0.9 ^{††}	-0.1 ± 1.4	-3.1 ± 1.0 ^{††}
Between-group difference in change after 12 weeks		-4.4 ± 1.1 ^{**}		-3.0 ± 1.8
Clinic SBP, mm Hg				
Baseline	143.6 ± 2.3	141.0 ± 2.6	140.3 ± 14.4	141.9 ± 3.2
Week 12	139.4 ± 2.3	131.0 ± 2.7	149.0 ± 4.4	132.1 ± 3.3
Change after 12 weeks	-4.2 ± 2.1 [†]	-10.1 ± 2.3 ^{††}	8.7 ± 3.8 [†]	-9.7 ± 2.7 ^{††}
Between-group difference in change after 12 weeks		-5.8 ± 3.1		-18.4 ± 4.7 ^{**}
Clinic DBP, mm Hg				
Baseline	76.7 ± 1.4	76.2 ± 1.7	78.1 ± 2.8	77.5 ± 2.0
Week 12	73.6 ± 1.4	73.7 ± 1.7	83.8 ± 2.8	73.6 ± 2.1
Change after 12 weeks	-3.0 ± 1.1 ^{††}	-2.5 ± 1.3	5.7 ± 2.1 ^{††}	-4.0 ± 1.5 ^{††}
Between-group difference in change after 12 weeks		0.6 ± 1.7		-9.6 ± 2.6 ^{**}
HbA1c, %				
Baseline	6.73 ± 0.12	6.77 ± 0.14	6.32 ± 0.23	6.48 ± 0.17
End of the study	6.75 ± 0.12	6.52 ± 0.14	6.57 ± 0.23	6.19 ± 0.17
Week 12	0.02 ± 0.06	-0.24 ± 0.07 ^{††}	0.26 ± 0.11 [†]	-0.28 ± 0.08 ^{††}
Between-group difference in change after 12 weeks		-0.26 ± 0.09 ^{**}		-0.54 ± 0.13 ^{**}
BW, kg				
Baseline	64.7 ± 1.6	66.0 ± 1.9	61.4 ± 3.2	64.7 ± 2.4
Week 12	64.3 ± 1.6	64.3 ± 1.9	61.7 ± 3.2	63.3 ± 2.4
Change after 12 weeks	-0.4 ± 0.2 [†]	-1.7 ± 0.2 ^{††}	0.3 ± 0.4	-1.5 ± 0.3 ^{††}
Between-group difference in change after 12 weeks		-1.3 ± 0.3 ^{**}		-1.7 ± 0.5 ^{**}
eGFR, ml/min/1.73 m ²				
Baseline	69.0 ± 2.1	69.7 ± 2.4	71.5 ± 4.0	68.5 ± 2.9

(Continues)

Table 2 (Continued)

	Aged <75 years		Aged ≥75 years	
	Placebo (n = 49)	Empagliflozin (n = 38)	Placebo (n = 14)	Empagliflozin (n = 30)
Week 12	67.8 ± 2.1	65.7 ± 2.4	71.4 ± 4.0	64.8 ± 3.0
Change after 12 weeks	-1.2 ± 1.1	-4.0 ± 1.3 ^{††}	-0.1 ± 2.0	-3.7 ± 1.4 [†]
Between-group difference in change after 12 weeks		-2.8 ± 1.7		-3.6 ± 2.5
Uric acid, mg/dl				
Baseline	5.17 ± 0.21	5.26 ± 0.24	6.00 ± 0.40	5.67 ± 0.29
Week 12	5.14 ± 0.21	4.65 ± 0.24	5.52 ± 0.40	4.90 ± 0.30
Change after 12 weeks	-0.03 ± 0.11	-0.62 ± 0.12 ^{††}	-0.48 ± 0.20 [†]	-0.77 ± 0.14 ^{††}
Between-group difference in change after 12 weeks		-0.59 ± 0.16 ^{**}		-0.29 ± 0.24

Abbreviations: BW, body weight; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration; HbA1c, glycosylated hemoglobin; PR, pulse rate; SBP, systolic blood pressure.

[†]*P* < .05.

^{††}*P* < .01 for comparisons between baseline and the end of 12 weeks of each treatment.

**P* < .05.

***P* < .01 for comparisons between placebo and empagliflozin treatment in change from baseline to week 12.

TABLE 3 Adverse events

Period	Group	Overall	<75 years	≥75 years
Run-in	All	5 (4)	5 (4)	0 (0)
Treatment	Placebo	4 (4)	3 (3)	1 (1)
	Empagliflozin	14 (8)	6 (4)	8 (4)

Note: Data are number of events (number of participants).

12, respectively), and there was marginally significant placebo-subtracted difference between the groups (-0.26% vs. -0.54% at week 12, respectively, *p* = .078) (Table 2).

The changes between baseline and week 12 in BW were -1.7 kg for participants taking empagliflozin who were aged <75 years vs. -1.5 kg for those aged ≥75 years, and these changes were similar in the two groups (Table 2). There was no significant placebo-subtracted difference in BW between the groups (<75 years: -1.3 kg, ≥75 years: -1.7 kg at week 12, respectively, *p* = .439).

There were significant reductions in eGFR in participants taking empagliflozin during the study (Table 2). However, there was a larger reduction in serum uric acid concentration between baseline and week 12 during empagliflozin treatment in both the <75 and ≥75 years groups (-0.62 vs. -0.77 mg/dl, respectively) (Table 2). In addition, there was no significant placebo-subtracted difference in serum uric acid concentration between the groups (<75 years: -0.59 mg/dl, ≥75 years: -0.29 mg/dl, at week 12, respectively, *p* = .302).

3.4 | Safety

Safety was assessed using the safety analysis dataset (Tables 3 and 4). No serious AEs occurred in either treatment or age group

(empagliflozin vs. placebo: six vs. three events, respectively, in <75-year-olds and eight vs. one events in ≥75-year-olds). Four events in the empagliflozin group (one each of thirst, polyuria, lumbago, and constipation) and one event (heartburn) in the placebo group occurred among the <75-year-olds, and three events occurred in the empagliflozin group (one each of genital itching, fatigue, and nausea) and no events in the placebo group among the ≥75-year-olds. There were no episodes of hypotension, dehydration, urinary tract infection, or acute kidney injury in either group. There were also no episodes of postural hypotension in either group.

4 | DISCUSSION

Here, we report the results of analyses of the efficacy and safety of empagliflozin in non-severely obese, elderly diabetic patients with uncontrolled nocturnal hypertension. The addition of empagliflozin to the therapeutic regimen of elderly diabetic patients was associated with similar significant reductions in 24-h ambulatory, daytime, morning home, and clinic BP to those that occurred in younger patients with T2DM.

The 2017 American College of Cardiologists (ACC)/American Hypertension Association (AHA) Hypertension Clinical Practice Guidelines recommend an SBP target of <130 mm Hg for elderly hypertensive patients.¹⁹ However, attention must be paid to the rate of reduction in the BP of elderly patients: An excessive reduction should be avoided. Although there were a few minor AEs, empagliflozin treatment did not increase the incidence of symptoms of hypotension or cause excessive BP lowering in the present study.

There were substantial reductions in 24-h BP, daytime BP, morning home BP, and clinic BP during empagliflozin treatment in both the <75 and ≥75 years groups. However, the reduction in

TABLE 4 Causal relationships

Group	Adverse event	Overall	<75 years	≥75 years
Placebo	Heartburn	1	1	0
Empagliflozin	Thirst	1	1	0
	Polyuria	1	1	0
	Lumbago	1	1	0
	Genital itching	1	0	1
	Fatigue	1	0	1
	Nausea	1	0	1
	Constipation	1	1	0

Note: Data are number of events (number of participants).

placebo-subtracted nighttime ambulatory SBP that was associated with empagliflozin treatment for 12 weeks in the ≥75 years group was -4.3 mm Hg, which was not significantly different from the change in the <75 years group ($p = .884$). Nevertheless, this nighttime BP reduction may be a potential mechanism for the cardioprotective action of SGLT2 inhibitors because the reduction in nighttime BP may synergize with a treatment-related reduction in blood volume²⁰ (suggested by an increase in hematocrit during empagliflozin treatment in the EMPA-REG OUTCOME trial¹⁵). In addition, the results of the SPRINT sub-analysis demonstrated the benefit of strict blood pressure control, with a low target blood pressure, in high-risk patients with hypertension who are ≥75 years of age.²¹ Therefore, the reductions in 24-h BP, morning home BP, and clinic BP, as well as in nighttime BP that occur during empagliflozin treatment would be expected to reduce the risks of major cardiovascular events and heart failure, regardless of age.

Similar reductions in HbA1c occurred in the present study in the two age groups. Moreover, no serious hypoglycemia occurred during empagliflozin treatment. In Japan, new guidelines for the treatment of diabetes in older individuals have been formulated on the basis of the “Glycemic Targets for Elderly Patients with Diabetes.” In these guidelines, older adults were placed into three categories according to their cognitive function and activities of daily living, and their target HbA1c was set according to whether or not drugs were being used that might cause severe hypoglycemia (insulin, sulfonylureas [SUs], and glinides).²² Hypoglycemia, which is a risk factor for dementia, depression, fracture, and cognitive decline in elderly patients with diabetes, can be recognized using self-monitoring of blood glucose (SMBG).²² Although blood glucose concentration was not measured across whole days using tools such as SMBG or continuous glucose monitoring in the present study, that SUs and insulin were not being used by participants in the study may have helped them avoid hypoglycemia.

There were no serious AEs in either the older or younger participants in the present study, probably because although the participants in the SACRA study were elderly (mean age approximately 70 years), they had good glycemic control (mean HbA1c 6.6%), and were selected on the basis of the presence of nocturnal hypertension only. In addition, as this is a post hoc analysis, the number of subjects was small, and the short-term of this study may

have also affected the results. Treatment with SGLT2 inhibitors reportedly requires caution because of the relatively high incidences of urinary tract infection, postural hypotension, or cerebral infarction as a result of dehydration, ketoacidosis, and frailty, which are consequences of their mode of action.^{23,24} In particular, many consider that the administration of SGLT2 inhibitors to elderly patients, who are less likely to notice symptoms of dehydration, should be limited.^{25,26} Several post-marketing surveillance studies have been conducted in elderly patients with T2DM who had been treated using SGLT2 inhibitors.²⁷⁻²⁹ In these studies, the incidences of AEs were quite low, and serious AEs, such as urinary tract infection, dehydration, hypoglycemia, and cerebral infarction, were very rare. Moreover, real-world evidence of efficacy and safety has been collected in a group of elderly patients with T2DM who had suboptimal glycemic control.³⁰ Most recent trials of SGLT2 inhibitors for efficacy of reduction in heart failure incidence or renal outcome have enrolled not only diabetic patients but also non-diabetic patients.^{31,32} In those studies, there was no significant difference in safety between diabetic and non-diabetic patients. Use of an SGLT2 inhibitor in elderly patients provides obvious clinical benefits, including reductions in HbA1c, BW, and BP, and appears to be both safe and effective, with low rates of AEs and hypoglycemic events being reported in elderly patients.

4.1 | Limitations

This was an exploratory sub-analysis of SACRA study data, which were obtained for particular age groups. Therefore, the most important limitation of the present study was the lack of power. The elderly subjects were also well selected and may have no serious adverse events in a short period of study. This study may not be easily applicable to a more frail elderly in the population.

4.2 | Conclusion

Treatment with an SGLT2 inhibitor, empagliflozin, is well tolerated overall in elderly patients with T2DM and improves blood pressure and blood glucose. The safety profile of the SACRA study was similar

to those of previous clinical and real-world studies, and new safety concerns were not identified. The minor AEs, such as higher urinary frequency, genital mycotic infection, and urinary tract infection, do not discourage the use of SGLT2 inhibitors in elderly patients with T2DM. The favorable effects of empagliflozin on blood pressure may be helpful in the treatment of diabetes, and especially for elderly patients with T2DM.

ACKNOWLEDGEMENTS

The authors would like to acknowledge all the patients, physicians (Naoko Tomitani, Masafumi Nishizawa, Tetsuro Yoshida, Mitsuyoshi Yamamoto, Kazuo Eguchi, Atsushi Mizuno, Shigeru Nakano, and Yuta Kemi), and medical staff who supported this study. We also thank Ms Chie Iwashita for the coordination and data management of the study. The independent study control center was managed, and all data were collected, by a contract research organization (Satt Co., Ltd., Tokyo, Japan). The authors would like to thank Kyouichi Wada and Azusa Kaneko for their assistance. We also thank Mark Cleasby, PhD, from Edanz Group (<https://en-author-services.edanzgroup.com/ac>) for editing drafts of this manuscript.

CONFLICT OF INTEREST

Kazuomi Kario has received research grants from Tanabe Mitsubishi Pharma Corporation. Kenta Okada has received scholarship funding from Daiichi Sankyo Co. and an honorarium from Sanofi KK. All other authors have no conflicts of interest to declare. Medical writing assistance was provided by Mark Cleasby, PhD, independent medical writer.

AUTHOR CONTRIBUTIONS

Kario K takes primary responsibility for this paper. Hoshide S and Kanegae H did the statistical analysis. Okada K wrote the manuscript. Okada K and Kato M collected the patients' data. Kario K acquired research grants for the SACRA study. Okada K, Hoshide S, Kato M, Kanegae H, Ishibashi S, and Kario K reviewed/edited the manuscript.

FUNDING INFORMATION

This study was funded by the Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance. Empagliflozin and placebo were provided by Boehringer Ingelheim.

ORCID

Satoshi Hoshide  <https://orcid.org/0000-0001-7541-5751>

Kazuomi Kario  <https://orcid.org/0000-0002-8251-4480>

REFERENCES

- Charvat H, Goto A, Goto M, et al. Impact of population aging on trends in diabetes prevalence: a meta-regression analysis of 160,000 Japanese adults. *J Diabetes Investg*. 2015;6(5):533-542.
- Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. *JAMA Intern Med*. 2014;174(2):251-258.
- Geller AI, Shehab N, Lovegrove MC, et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. *JAMA Intern Med*. 2014;174(5):678-686.
- Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care*. 2012;35(12):2650-2664.
- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38(1):140-149.
- Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet*. 2006;368(9529):29-36.
- Meneilly GS, Knip A, Tessier D. Diabetes in the elderly. *Can J Diabetes*. 2013;37(Suppl 1):S184-S190.
- Sinclair A, Morley J. Frailty and diabetes. *Lancet*. 2013;382(9902):1386-1387.
- Astrup AS, Nielsen FS, Rossing P, et al. Predictors of mortality in patients with type 2 diabetes with or without diabetic nephropathy: a follow-up study. *J Hypertens*. 2007;25(12):2479-2485.
- Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin Sci*. 2001;101(6):671-679.
- Rawshani A, Rawshani A, Franzén S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2018;379(7):633-644.
- Bouhanick B, Bongard V, Amar J, Bousquel S, Chamontin B. Prognostic value of nocturnal blood pressure and reverse-dipping status on the occurrence of cardiovascular events in hypertensive diabetic patients. *Diabetes Metab*. 2008;34(6 Pt 1):560-567.
- Wijkman M, Länne T, Engvall J, Lindström T, Ostgren CJ, Nystrom FH. Masked nocturnal hypertension—a novel marker of risk in type 2 diabetes. *Diabetologia*. 2009;52(7):1258-1264.
- Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373(22):2103-2116.
- Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128.
- Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657.
- Kario K, Okada K, Kato M, et al. 24-hour blood pressure-lowering effect of an SGLT-2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: results from the randomized, placebo-controlled SACRA study. *Circulation*. 2018;139(18):2089-2097.
- Mizuno H, Hoshide S, Fukutomi M, Kario K. Differing effects of aliskiren/amlodipine combination and high-dose amlodipine monotherapy on ambulatory blood pressure and target organ protection. *J Clin Hypertens*. 2016;18(1):70-78.
- Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6):e113-e115.
- Kario K, Weber M, Ferrannini E. Nocturnal hypertension in diabetes: potential target of sodium/glucose cotransporter 2 (SGLT2) inhibition. *J Clin Hypertens*. 2018;20(3):424-428.
- Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥ 75 years: a randomized clinical trial. *JAMA*. 2016;315(24):2673-2682.

22. Japan Diabetes Society (JDS)/Japan Geriatrics Society (JGS) Joint Committee on Improving Care for Elderly Patients with Diabetes. Glycemic targets for elderly patients with diabetes. *Geriatr Gerontol Int*. 2016;16(12):1243-1245.
23. Mathieu C, Herrera Marmolejo M, González González JG, et al. Efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin over 52 weeks in patients with type 2 diabetes. *Diabetes Obes Metab*. 2016;18(11):1134-1137.
24. Grandy S, Sternhufvud C, Ryden A, Sugg J, Rohwedder K. Patient-reported outcomes among patients with type 2 diabetes mellitus treated with dapagliflozin in a triple-therapy regimen for 52 weeks. *Diabetes Obes Metab*. 2016;18(3):306-309.
25. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. *Drugs*. 2015;75(1):33-59.
26. Elmore LK, Baggett S, Kyle JA, Skelley JW. A review of the efficacy and safety of canagliflozin in elderly patients with type 2 diabetes. *Consult Pharm*. 2014;29(5):335-346.
27. Terauchi Y, Yokote K, Nakamura I, Sugamori H. Safety of ipragliflozin in elderly Japanese patients with type 2 diabetes mellitus (STELLA-ELDER): interim results of a post-marketing surveillance study. *Exp Opin Pharmacother*. 2016;17(4):463-471.
28. Goda M, Yamakura T, Sasaki K, Tajima T, Ueno M. Safety and efficacy of canagliflozin in elderly patients with type 2 diabetes mellitus: a 1-year post-marketing surveillance in Japan. *Curr Med Res Opin*. 2018;34(2):319-327.
29. Yokote K, Terauchi Y, Nakamura I, Sugamori H. Real-world evidence for the safety of ipragliflozin in elderly Japanese patients with type 2 diabetes mellitus (STELLA-ELDER): final results of a post-marketing surveillance study. *Expert Opin Pharmacother*. 2016;17(15):1995-2003.
30. Carretero Gómez J, Arévalo Lorigo JC, Gómez Huelgas R, et al. Combination therapy with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors in older patients with type 2 diabetes: a real-world evidence study. *Can J Diabetes*. 2019;43(3):186-192.
31. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995-2008.
32. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413-1424.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Okada K, Hoshide S, Kato M, Kanegae H, Ishibashi S, Kario K. Safety and efficacy of empagliflozin in elderly Japanese patients with type 2 diabetes mellitus: A post hoc analysis of data from the SACRA study. *J Clin Hypertens*. 2021;23:860-869. <https://doi.org/10.1111/jch.14131>