Dapagliflozin and Blood Pressure in Patients with Chronic Kidney Disease and Albuminuria

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Abstract

Background and Aims Sodium–glucose cotransporter 2 inhibitors decrease blood pressure in patients with type 2 diabetes, but the consistency and magnitude of blood pressure lowering with dapagliflozin in patients with chronic kidney disease (CKD) is unknown. We conducted a prespecified analysis of the DAPA-CKD trial to investigate the effect of dapagliflozin on systolic blood pressure (SBP) in patients with CKD, with and without type 2 diabetes.

Methods A total of 4304 adults with baseline estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73m² and urinary albumin-to-creatinine ratio (UACR) 200-5000 mg/g were randomized to either dapagliflozin 10 mg or placebo once daily; median follow-up was 2.4 years. The primary endpoint was a composite of sustained ≥50% eGFR decline, end-stage kidney disease, or death from a kidney or cardiovascular cause. Change in SBP was a prespecified outcome.

Results Baseline mean (SD) SBP was 137.1 mmHg (17.4). By Week 2, dapagliflozin compared to placebo reduced SBP by 3.6 mmHg (95% CI 2.8-4.4 mmHg), an effect maintained over the duration of the trial (2.9 mmHg, 2.3-3.6 mmHg). Time-averaged reductions in SBP were 3.2 mmHg (2.5-4.0 mmHg) in patients with diabetes and 2.3 mmHg (1.2-3.4 mmHg) in patients without diabetes. The time-averaged effect of dapagliflozin on diastolic blood pressure (DBP) was 1.0 mmHg (0.6-1.4 mmHg); 0.8 mmHg (0.4-1.3 mmHg) in patients with diabetes and 1.4 mmHg (0.7-2.1 mmHg) in patients without diabetes. Benefits of dapagliflozin on the primary composite and secondary endpoints were evident across the spectrum of baseline SBP and DBP.

Conclusion In patients with CKD and albuminuria, randomization to dapagliflozin was associated with modest reductions in systolic and diastolic BP. (Am Heart J 2024;270:125–135.)

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Background

Hypertension is common among patients with chronic kidney disease (CKD). According to the United States Renal Data System (USRDS), more than 90% of patients with CKD have arterial hypertension and frequently develop associated complications;[1] data from international registries suggest similarly high prevalence of hypertension in other regions.[2,3] The relation between blood pressure and CKD is bi-directional. It is well established that persistent, severe elevations in blood pressure can result in impaired kidney function as well as widespread arteriosclerotic vascular disease; hypertension of variable duration and severity is commonly observed, with or without evidence of hypervolemia, as a consequence of CKD. Attenuation of arterial hypertension is an essential management goal for the treatment of CKD to reduce the risk

of cardiovascular complications, including heart failure, stroke, and arrhythmia, including atrial fibrillation, ventricular ectopy, and sudden death.[4,5]

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have emerged as a potent therapy to reduce the risk of progressive kidney disease and cardiovascular events in patients with CKD.[6,7] These agents reduce absorption of glucose and sodium in the proximal tubule, thereby increasing glycosuria and diuresis, typically reducing intravascular volume which can contribute to a reduction in blood pressure.[8] Treatment with SGLT2 inhibitors has consistently been associated with reduction in blood pressure in clinical trials enrolling patients with type 2 diabetes, the majority of whom have had preserved kidney function.[9] The consistency and magnitude of blood pressure lowering effects of SGLT2 inhibitors in a broad population of patients with CKD, with and without type 2 diabetes, have not been well established.

We performed a prespecified analysis of data from the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial to investigate the effects of the SGLT2 inhibitor dapagliflozin on systolic and diastolic blood pressures (SBP and DBP) and to determine whether the effects of dapagliflozin on kidney, cardiovascular and safety outcomes were consistent across the spectrum of baseline blood pressure values.

Methods

Study design

DAPA-CKD was a randomized, double-blind, placebo-controlled, multicentre clinical trial (clinicaltrials.gov/study/NCT03036150); manuscripts describing trial design, baseline characteristics, primary results, effects on estimated glomerular filtration rate (eGFR) slope and albuminuria, and effects stratified by diabetes status and other clinical characteristics have been previously published.[6,10-14] The trial was conducted at 386 sites in 21 countries from February 2017 through June 2020. All participants provided written informed consent before any study-specific procedure commenced. Participant safety was overseen by an independent data and safety monitoring committee.

Participants

Adults with or without type 2 diabetes, with eGFR 25-75 mL/min/1.73m^2 and urinary albumin-to-creatinine ratio (UACR) 200-5000 mg/g were eligible for participation. We required participants to be treated with a stable maximally tolerated dose of renin-angiotensin-aldosterone system (RAAS) inhibitor for ≥ 4 weeks unless medically contraindicated. Key exclusion criteria included documented diagnosis of type 1 diabetes, polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody-associated vasculitis. A complete list of inclusion and exclusion criteria and the trial protocol have been previously published.[6,11,14]

Procedures

Participants were randomly assigned to dapagliflozin 10 mg once daily or matching placebo, in accordance with the sequestered, fixed-randomization schedule, with the use of balanced blocks to ensure an approximate 1:1 ratio of the 2 regimens. Randomization was stratified by diabetes status (yes or no) and UACR ($\leq$ or >1000 mg/g). After randomization, in-person study visits were performed after 2 weeks, 2, 4, and 8 months and at 4-month intervals thereafter. At each follow-up visit, study personnel recorded vital signs, obtained blood and urine samples, and recorded information on potential study endpoints, adverse events (AEs), concomitant therapies, and study drug adherence.

Endpoints

Primary composite endpoint was time to $\geq 50\%$ decline in eGFR (confirmed by a second serum creatinine measurement after at least 28 days), onset of kidney failure (defined as maintenance dialysis for at least 28 days, kidney transplantation, or eGFR <15 mL/min/1.73m^2 confirmed by a second measurement after at least 28 days), or death from kidney or cardiovascular cause. Secondary endpoints were time to: (1) a composite kidney endpoint of $\geq 50\%$ sustained decline in eGFR, kidney failure or death from kidney disease; (2) a composite cardiovascular endpoint defined as hospitalization for heart failure or cardiovascular death; and (3) death from any cause. All efficacy endpoints were adjudicated by a masked, independent Clinical Events Committee, except for quantitative assessments of eGFR which were obtained from our central laboratory. Change in systolic blood pressure (SBP) was a prespecified outcome.

Safety

Given extensive prior experience with dapagliflozin, we limited our ascertainment of AEs to serious AEs (SAEs), AEs resulting in the discontinuation of study drug, and AEs of special interest (symptoms of volume depletion, kidney disease events, major hypoglycemia, bone fractures, amputations, potential diabetic ketoacidosis).

Statistical analysis

All analyses presented here followed the intention-to-treat principle. We compared short-term (2 weeks) and time-averaged effects of dapagliflozin and placebo on SBP and DBP, adjusting for factors affecting randomization (presence of diabetes and UACR <1000 or ≥ 1000 mg/g) and baseline SBP. We analyzed the time-averaged effects of dapagliflozin on SBP and DBP by fitting repeated measures models using restricted maximum likelihood.

These models included categorical fixed effects for treatment, visit, and 3-way interaction term between baseline SBP and DBP category, visit, and treatment assignment. We utilized an unstructured variance-covariance matrix that allows for a general pattern of (SD) and correlations for SBP and DBP determinations at different timepoints. We conducted time-to-event analyses using proportional hazards (Cox) regression stratified by factors affecting randomization (diabetes status and UACR) and adjusted for baseline eGFR, yielding hazard ratios (HR) and 95% confidence intervals (95% CI) calculated from model parameter coefficients and SE, respectively. To explore whether the effects of dapagliflozin on primary composite and secondary endpoints were modified by the presence and/or severity of hypertension, we stratified participants according to the following categories of SBP: <120, 120 to <130, 130 to <140, 140 to <150, and ≥150 mmHg. We compared results across the spectrum of SBP by including a multiplicative interaction term between randomized treatment group and SBP category. We conducted a companion analysis in which we stratified participants by presence or absence of resistant hypertension at baseline (defined as use of three or more antihypertensive agents including 1 or more diuretic agents or 4 or more antihypertensive agents of any class) and another in which we considered SBP as a continuous variable, and completed the same for DBP. For all analyses of effect modification, we assessed for nonuniformity of HRs with Akaike's information criterion.

We performed exploratory analyses additionally stratified by the presence or absence of diabetes and categories of baseline eGFR and UACR. We considered P-value <.05 to be statistically significant. We performed all analyses with SAS version 9.4 (SAS Institute) or R version 4.0.2 (R Foundation).

Results

Of the 4304 participants in the DAPA-CKD trial (2152 randomized to each dapagliflozin and placebo), 4303 (99.9%) had data available on baseline blood pressure. Table 1 shows baseline characteristics by baseline SBP categories (<120, 120−<130, 130−<140, 140−<150, and ≥150 mmHg). Participants with higher baseline SBP had higher UACR and were more likely to have a history of cardiovascular disease.

Effects of dapagliflozin on SBP

Figure 1 shows changes in SBP over time. At Week 2, mean SBP was 3.6 mmHg (95% CI 2.8-4.4 mmHg) lower in patients randomized to dapagliflozin compared to those randomized to placebo, an effect that was largely maintained over the duration of the trial (2.9 mmHg [95%CI 2.3-3.6 mmHg]); Figure 1, **panel A**). Time-averaged reductions in SBP were 3.2 mmHg (2.5-4.0 mmHg) in patients with diabetes and 2.3 mmHg

Figure 1. Changes in SBP over time and as stratified by the presence type 2 diabetes. SBP, systolic blood pressure.
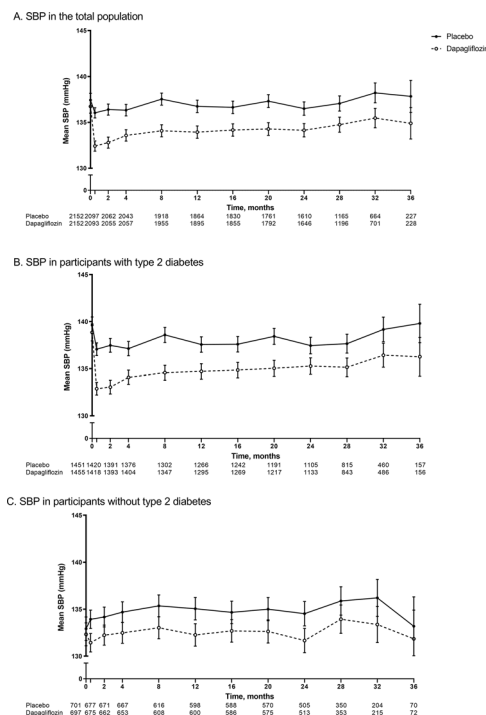
(1.2-3.4 mmHg) in patients without diabetes (interaction P = .50). (Figure 1, panels B and C). Figure 2 shows the effect of dapagliflozin on mean SBP across several pre-specified subgroups, as well as by baseline SBP, and by the presence or absence of resistant hypertension.

Effects of dapagliflozin on DBP

Figure 3 shows changes in DBP over time. At Week 2, mean DBP was 1.5 mmHg (1.1-2.0 mmHg) lower in patients randomized to dapagliflozin compared to those randomized to placebo, an effect that was partially maintained over the duration of the trial (1.0 mmHg [0.6-1.4 mmHg]; Figure 3, panel A). In contrast to effects on SBP, where the blood pressure lowering effects of dapagliflozin in patients with diabetes were numerically larger, the time-averaged effect of dapagliflozin on DBP was 0.8 mmHg (0.4-1.3 mmHg) in patients with diabetes and 1.4 mmHg (0.7-2.1 mmHg) in patients without diabetes (P = .36). (Figure 3, panels B and C).

Effects of dapagliflozin on primary composite and secondary endpoints by baseline SBP
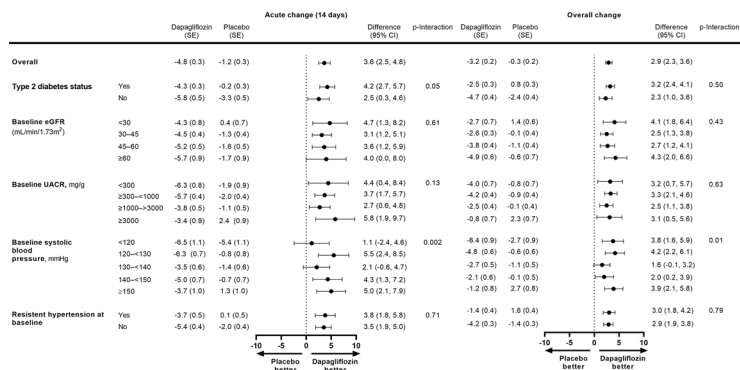
Figure 4 shows a forest plot of the primary composite and secondary endpoints by baseline SBP categories and by presence or absence of resistant hypertension at baseline. The effects of dapagliflozin were consistent among participants across the range of SBP; the reason(s) for

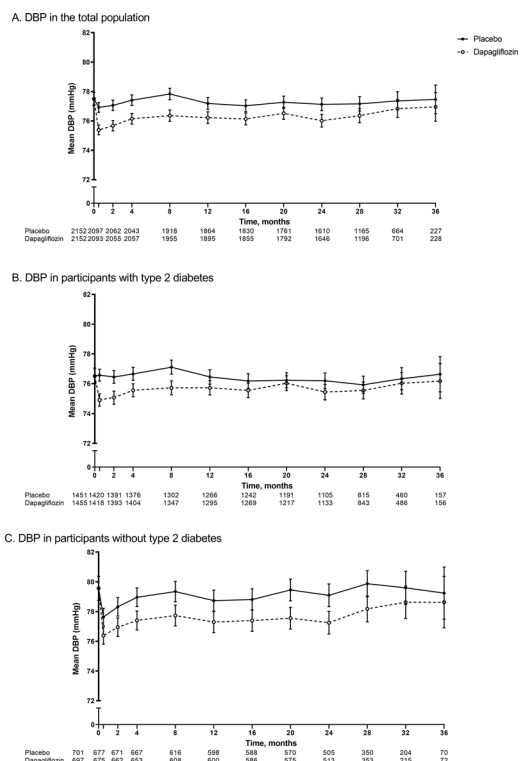**Table 1.** Baseline characteristics by SBP categories.

	SBP<120 (n = 630)		SBP 120 to <130 (n = 807)		SBP 130 to <140 (n = 1095)		SBP 140 to <150 (n = 859)		SBP≥150 (n = 913)	
	Dapagliflozin N = 321	Placebo N = 309	Dapagliflozin N = 426	Placebo N = 381	Dapagliflozin N = 535	Placebo N = 560	Dapagliflozin N = 417	Placebo N = 442	Dapagliflozin N = 453	Placebo N = 460
Age – year	57.8 (13.3)	56.9 (13.8)	59.8 (13.0)	59.3 (12.9)	62.4 (12.0)	61.8 (11.3)	63.2 (11.3)	64.2 (11.1)	64.5 (9.7)	65.3 (10.6)
Female sex – n (%)	117 (36.4)	110 (35.6)	146 (34.3)	121 (31.8)	177 (33.1)	180 (32.1)	125 (30.0)	153 (34.6)	144 (31.8)	152 (33.0)
Race – n (%)										
Asian	166 (51.7)	144 (46.6)	176 (41.3)	143 (37.5)	176 (32.9)	200 (35.7)	124 (29.7)	134 (30.3)	107 (23.6)	97 (21.1)
Black or African American	15 (4.7)	8 (2.6)	14 (3.3)	13 (3.4)	18 (3.4)	28 (5.0)	23 (5.5)	17 (3.8)	34 (7.5)	21 (4.6)
White	122 (38.0)	140 (45.3)	197 (46.2)	201 (52.8)	302 (56.4)	298 (53.2)	236 (56.6)	246 (55.7)	267 (58.9)	281 (61.1)
Other	18 (5.6)	17 (5.5)	39 (9.1)	24 (6.3)	39 (7.3)	34 (6.1)	34 (8.1)	45 (10.2)	45 (9.9)	61 (13.3)
Body mass index (kg/m^2)	28.0 (6.5)	27.4 (5.8)	28.3 (5.7)	29.3 (6.2)	29.5 (5.8)	30.0 (6.4)	30.4 (6.0)	30.2 (6.1)	30.3 (5.9)	30.5 (6.3)
Current smoker – n (%)	40 (12.5)	42 (13.6)	64 (15.0)	61 (16.0)	58 (10.8)	87 (15.5)	58 (13.9)	47 (10.6)	63 (13.9)	64 (13.9)
Blood pressure – mmHg										
Systolic	111.1 (7.0)	112.2 (6.7)	125.0 (2.9)	125.0 (2.9)	134.6 (3.0)	134.4 (3.0)	144.2 (2.9)	144.0 (3.0)	161.6 (11.0)	162.1 (11.5)
Diastolic	68.7 (8.9)	69.8 (8.2)	75.5 (8.4)	75.4 (7.7)	77.6 (9.1)	77.8 (8.3)	80.3 (10.2)	79.3 (9.6)	83.0 (11.4)	82.3 (12.5)
eGFR – mL/min/1.73m^2	43.2 (12.4)	41.8 (11.8)	44.4 (12.4)	43.5 (11.9)	43.4 (11.9)	43.5 (12.7)	41.9 (12.1)	43.5 (13.0)	43.2 (12.7)	42.2 (12.1)
HbA1c – %	6.8 (1.8)	6.7 (1.8)	6.8 (1.7)	7.0 (1.8)	7.3 (1.8)	7.1 (1.7)	7.2 (1.7)	7.1 (1.6)	7.2 (1.7)	7.2 (1.7)
UACR (Q1–Q3)	697 (402, 1363)	682 (408, 1240)	796 (395, 1619)	791 (435, 1574)	923 (443, 1792)	907 (465, 1811)	1105 (541, 2117)	953 (508, 1973)	1282 (573, 2606)	1388 (662, 2426)
UACR >1000 mg/g – n (%)	113 (35.2)	110 (35.6)	183 (43.0)	159 (41.7)	256 (47.8)	257 (45.9)	227 (54.4)	217 (49.1)	269 (59.4)	288 (62.6)
Type 2 diabetes – n (%)	173 (53.9)	151 (48.9)	249 (58.4)	236 (61.9)	382 (71.4)	386 (68.9)	304 (71.9)	327 (74.0)	347 (76.6)	351 (76.3)
Duration of diabetes – year (Q1–Q3)	13.0 (6.5, 21.1)	14.6 (8.0, 20.2)	11.6 (6.1, 18.6)	13.1 (7.7, 19.4)	13.9 (7.0, 20.8)	12.9 (6.8, 19.6)	14.2 (6.8, 21.3)	14.2 (7.7, 21.1)	15.2 (8.4, 20.9)	15.6 (7.9, 21.6)
CV disease – n (%)	98 (30.5)	93 (30.1)	135 (31.7)	121 (31.8)	217 (40.6)	213 (38.0)	180 (43.2)	175 (39.6)	183 (40.4)	195 (42.4)
Prior medication – n (%)										
ACE inhibitor/ARB	312 (97.2)	299 (96.8)	420 (98.6)	370 (97.1)	525 (98.1)	550 (98.2)	409 (98.1)	427 (96.6)	446 (98.4)	451 (98.0)
Diuretic	108 (33.6)	109 (35.3)	168 (39.4)	156 (40.9)	221 (41.3)	236 (42.1)	183 (43.9)	212 (48.0)	248 (54.7)	241 (52.4)
Insulin*	95 (54.9)	79 (52.3)	130 (52.2)	132 (55.9)	215 (56.3)	198 (51.3)	173 (56.9)	169 (51.7)	201 (57.9)	206 (58.7)

* in participants with diabetes. Data are represented as mean (SD) unless indicated otherwise. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; CV, cardiovascular; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; UACR, urinary albumin-creatinine ratio.

Figure 2. Effect of dapagliflozin on mean SBP across prespecified subgroups. eGFR, estimated glomerular filtration rate; systolic blood pressure; UACR, urinary-albumin-to-creatinine.

		Acute change (14 days)				Overall change			
		Dapagliflozin (SE)	Placebo (SE)	Difference (95% CI)	p-Interaction	Dapagliflozin (SE)	Placebo (SE)	Difference (95% CI)	p-Interaction
Overall		-4.8 (0.3)	-1.2 (0.3)	3.6 (2.5, 4.8)		-3.2 (0.2)	-0.3 (0.2)	2.9 (2.3, 3.6)	
Type 2 diabetes status	Yes	-4.3 (0.3)	-0.2 (0.3)	4.2 (2.7, 5.7)	0.05	-2.5 (0.3)	0.8 (0.3)	3.2 (2.4, 4.1)	0.50
	No	-5.8 (0.5)	-3.3 (0.5)	2.5 (0.3, 4.6)		-4.7 (0.4)	-2.4 (0.4)	2.3 (1.0, 3.6)	
Baseline eGFR (mL/min/1.73m²)	<30	-4.3 (0.8)	0.4 (0.7)	4.7 (1.3, 8.2)	0.61	-2.7 (0.7)	1.4 (0.6)	4.1 (1.8, 6.4)	0.43
	30–45	-4.5 (0.4)	-1.3 (0.4)	3.1 (1.2, 5.1)		-2.6 (0.3)	-0.1 (0.4)	2.5 (1.3, 3.8)	
	45–60	-5.2 (0.5)	-1.6 (0.5)	3.6 (1.2, 5.9)		-3.8 (0.4)	-1.1 (0.4)	2.7 (1.2, 4.1)	
	≥60	-5.7 (0.9)	-1.7 (0.9)	4.0 (0.8, 8.0)		-4.9 (0.6)	-0.6 (0.7)	4.3 (2.0, 6.6)	
Baseline UACR, mg/g	<300	-6.3 (0.8)	-1.9 (0.8)	4.4 (0.4, 8.4)	0.13	-4.0 (0.7)	-0.8 (0.7)	3.2 (0.7, 5.7)	0.63
	≥300–<1000	-5.7 (0.4)	-2.0 (0.4)	3.7 (1.7, 5.7)		-4.2 (0.4)	-0.9 (0.4)	3.3 (2.1, 4.6)	
	≥1000–>3000	-3.8 (0.5)	-1.1 (0.5)	2.7 (0.6, 4.8)		-2.5 (0.4)	-0.1 (0.4)	2.5 (1.1, 3.8)	
	≥3000	-3.4 (0.9)	2.4 (0.9)	5.8 (1.9, 9.7)		-0.8 (0.7)	2.3 (0.7)	3.1 (0.5, 5.6)	
Baseline systolic blood pressure, mmHg	<120	-6.5 (1.1)	-5.4 (1.1)	1.1 (-2.4, 4.6)	0.002	-6.4 (0.9)	-2.7 (0.9)	3.8 (1.6, 5.9)	0.01
	120–<130	-6.3 (0.7)	-0.8 (0.7)	5.5 (2.4, 8.5)		-4.8 (0.6)	-0.6 (0.6)	4.2 (2.2, 6.1)	
	130–<140	-3.5 (0.6)	-1.4 (0.6)	2.1 (-0.8, 4.7)		-2.7 (0.5)	-1.1 (0.5)	1.6 (-0.1, 3.2)	
	140–<150	-5.0 (0.7)	-0.7 (0.7)	4.3 (1.3, 7.2)		-2.1 (0.6)	-0.1 (0.5)	2.0 (0.2, 3.9)	
	≥150	-3.7 (1.0)	1.3 (1.0)	5.0 (2.1, 7.9)		-1.2 (0.8)	2.7 (0.8)	3.9 (2.1, 5.8)	
Resistent hypertension at baseline	Yes	-3.7 (0.5)	0.1 (0.5)	3.8 (1.8, 5.8)	0.71	-1.4 (0.4)	1.6 (0.4)	3.0 (1.8, 4.2)	0.79
	No	-5.4 (0.4)	-2.0 (0.4)	3.5 (1.9, 5.0)		-4.2 (0.3)	-1.4 (0.3)	2.9 (1.9, 3.8)	

Figure 3. Changes in DBP over time and as stratified by type 2 diabetes status. DBP, diastolic blood pressure.

A. DBP in the total population

	0	2	4	8	12	16	20	24	28	32	36
Placebo	2152	2097	2062	2043	1918	1864	1830	1761	1610	1165	664	227
Dapagliflozin	2152	2093	2055	2057	1955	1895	1855	1792	1646	1196	701	228

B. DBP in participants with type 2 diabetes

	0	2	4	8	12	16	20	24	28	32	36
Placebo	1451	1420	1391	1376	1302	1266	1242	1191	1105	815	460	157
Dapagliflozin	1455	1418	1393	1404	1347	1295	1269	1217	1133	843	486	156

C. DBP in participants without type 2 diabetes

	0	2	4	8	12	16	20	24	28	32	36
Placebo	701	677	671	667	616	598	588	570	505	350	204	70
Dapagliflozin	697	675	662	653	608	600	586	575	513	353	215	72

the somewhat disparate results in one category (baseline SBP 140−<150 mmHg) are unknown and may be due to chance. Figure 5 shows the HR (dapagliflozin versus placebo) for the primary composite endpoint considering baseline SBP as a continuous variable in all participants (**panel A**) and participants with (**panel B**) and without (**panel C**) type 2 diabetes. These figures suggest a more pronounced benefit of dapagliflozin among par-

ticipants with lower baseline SBP, although there was no statistical evidence of heterogeneity. There was no additional effect modification on the primary composite endpoint by baseline eGFR (randomized treatment × baseline SBP × baseline eGFR; interaction $P = .96$) or baseline UACR (randomized treatment × baseline SBP × baseline UACR; interaction $P = .29$). Figure 6 shows the HR (dapagliflozin versus placebo) for the primary composite endpoint considering baseline DBP as a continuous variable in all participants (**panel A**) and participants with (**panel B**) and without (**panel C**) type 2 diabetes.
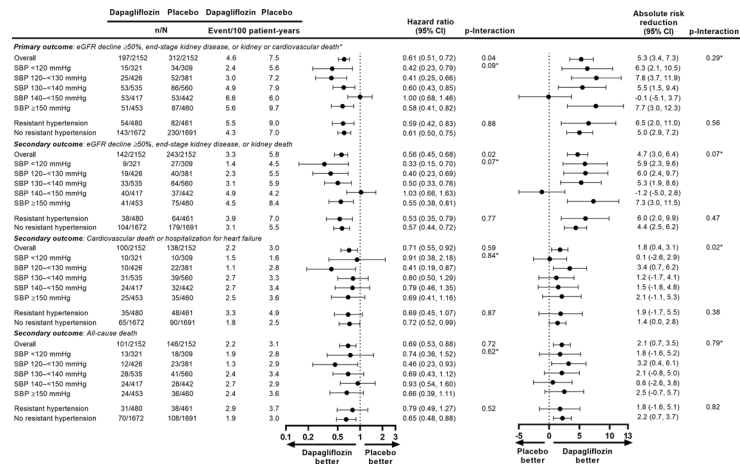
Safety

The risk of any SAE was similar between dapagliflozin and placebo and did not vary across baseline SBP categories (Table 2). There were no notable numerical imbalances in AEs related to volume depletion except among participants with baseline SBP <120 mmHg.
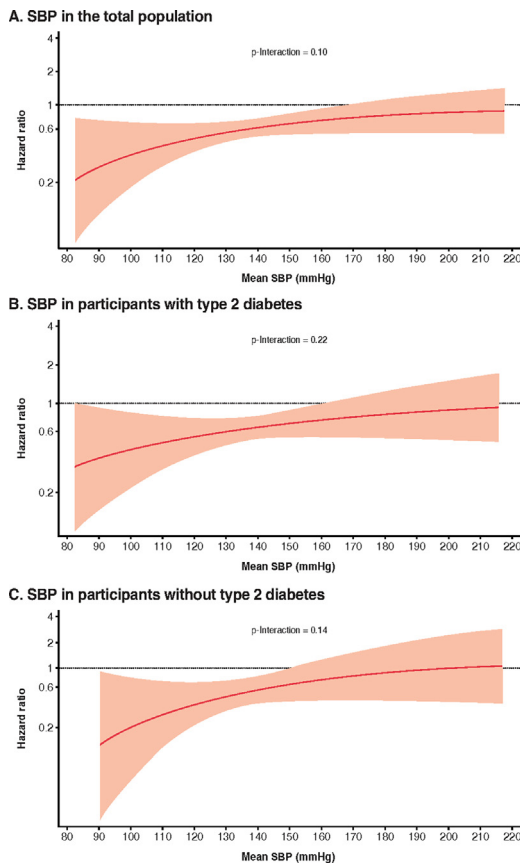
Discussion

In this prespecified analysis of data from the DAPA-CKD trial, we demonstrate that treatment with dapagliflozin results in a modest but clinically meaningful placebo-adjusted reduction in SBP, evident soon after initiation of therapy and maintained over the course of the trial. The magnitude reduction in SBP was similar to that provided by several commonly prescribed antihypertensive agents or following renal denervation.[15-19] There were small corresponding changes in DBP as well. The benefits of dapagliflozin on the primary endpoint – a composite of progressive kidney disease (including kidney failure) or death due to kidney or cardiovascular disease – as well as on all other secondary endpoints, were evident across the spectrum of baseline SBP and DBP.

These results confirm and extend previously published studies examining the effects of SGLT2 inhibitors on blood pressure.[20,21] In patients with type 2 diabetes,

Figure 4. Primary and secondary endpoints according to baseline SBP and by the presence or absence of resistant hypertension at baseline. *Continuous ordinal interaction. Absolute risk reduction rates are based on n/N%. eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

	Dapagliflozin n/N	Placebo n/N	Dapagliflozin Event/100 patient-years	Placebo Event/100 patient-years	Hazard ratio (95% CI)	p-Interaction	Absolute risk reduction (95% CI)	p-Interaction
Primary outcome: eGFR decline ≥50%, end-stage kidney disease, or kidney or cardiovascular death*								
Overall	197/2152	312/2152	4.6	7.5	0.61 (0.51, 0.72)	0.04	5.3 (3.4, 7.3)	0.29*
SBP <120 mmHg	15/321	34/309	2.4	5.6	0.42 (0.23, 0.79)	0.09*	6.3 (2.1, 10.5)	
SBP 120–<130 mmHg	25/426	52/381	3.0	7.2	0.41 (0.25, 0.66)		7.8 (3.7, 11.9)	
SBP 130–<140 mmHg	53/535	86/560	4.9	7.9	0.60 (0.43, 0.85)		5.5 (1.5, 9.4)	
SBP 140–<150 mmHg	53/417	53/442	6.6	6.0	1.00 (0.68, 1.46)		-0.1 (-5.1, 3.7)	
SBP ≥150 mmHg	51/453	87/460	5.6	9.7	0.58 (0.41, 0.82)		7.7 (3.0, 12.3)	
Resistant hypertension	54/480	82/461	5.5	9.0	0.59 (0.42, 0.83)	0.88	6.5 (2.0, 11.0)	0.56
No resistant hypertension	143/1672	230/1691	4.3	7.0	0.61 (0.50, 0.75)		5.0 (2.9, 7.2)	
Secondary outcome: eGFR decline ≥50%, end-stage kidney disease, or kidney death								
Overall	142/2152	243/2152	3.3	5.8	0.56 (0.45, 0.68)	0.02	4.7 (3.0, 6.4)	0.07*
SBP <120 mmHg	9/321	27/309	1.4	4.5	0.33 (0.15, 0.70)	0.07*	5.9 (2.3, 9.6)	
SBP 120–<130 mmHg	19/426	40/381	2.3	5.5	0.40 (0.23, 0.69)		6.0 (2.4, 9.7)	
SBP 130–<140 mmHg	33/535	64/560	3.1	5.9	0.50 (0.33, 0.76)		5.3 (1.9, 8.6)	
SBP 140–<150 mmHg	40/417	37/442	4.9	4.2	1.03 (0.66, 1.63)		-1.2 (-5.0, 2.6)	
SBP ≥150 mmHg	41/453	75/460	4.5	8.4	0.55 (0.38, 0.81)		7.3 (3.0, 11.5)	
Resistant hypertension	38/480	64/461	3.9	7.0	0.53 (0.35, 0.79)	0.77	6.0 (2.0, 9.9)	0.47
No resistant hypertension	104/1672	179/1691	3.1	5.5	0.57 (0.44, 0.72)		4.4 (2.5, 6.2)	
Secondary outcome: Cardiovascular death or hospitalization for heart failure								
Overall	100/2152	138/2152	2.2	3.0	0.71 (0.55, 0.92)	0.59	1.8 (0.4, 3.1)	0.02*
SBP <120 mmHg	10/321	10/309	1.5	1.6	0.91 (0.38, 2.18)	0.84*	0.1 (-2.6, 2.9)	
SBP 120–<130 mmHg	10/426	22/381	1.1	2.8	0.41 (0.19, 0.87)		3.4 (0.7, 6.2)	
SBP 130–<140 mmHg	31/535	39/560	2.7	3.3	0.80 (0.50, 1.29)		1.2 (-1.7, 4.1)	
SBP 140–<150 mmHg	24/417	32/442	2.7	3.4	0.79 (0.46, 1.35)		1.5 (-1.8, 4.8)	
SBP ≥150 mmHg	25/453	35/460	2.5	3.6	0.69 (0.41, 1.16)		2.1 (-1.1, 5.3)	
Resistant hypertension	35/480	48/461	3.3	4.9	0.69 (0.45, 1.07)	0.87	1.9 (-1.7, 5.5)	0.38
No resistant hypertension	65/1672	90/1691	1.8	2.5	0.72 (0.52, 0.99)		1.4 (0.0, 2.8)	
Secondary outcome: All-cause death								
Overall	101/2152	146/2152	2.2	3.1	0.69 (0.53, 0.88)	0.72	2.1 (0.7, 3.5)	0.79*
SBP <120 mmHg	13/321	18/309	1.9	2.8	0.74 (0.36, 1.52)	0.62*	1.8 (-1.6, 5.2)	
SBP 120–<130 mmHg	12/426	23/381	1.3	2.9	0.46 (0.23, 0.93)		3.2 (0.4, 6.1)	
SBP 130–<140 mmHg	28/535	41/560	2.4	3.4	0.69 (0.43, 1.12)		2.1 (-0.8, 5.0)	
SBP 140–<150 mmHg	24/417	28/442	2.7	2.9	0.93 (0.54, 1.60)		0.6 (-2.6, 3.8)	
SBP ≥150 mmHg	24/453	36/460	2.4	3.6	0.66 (0.39, 1.11)		2.5 (-0.7, 5.7)	
Resistant hypertension	31/480	38/461	2.9	3.7	0.79 (0.49, 1.27)	0.52	1.8 (-1.6, 5.1)	0.82
No resistant hypertension	70/1672	108/1691	1.9	3.0	0.65 (0.48, 0.88)		2.2 (0.7, 3.7)	

Figure 5. Spline curves for relationship treatment effects for primary outcome as function of baseline SBP. SBP, systolic blood pressure.

A. SBP in the total population

B. SBP in participants with type 2 diabetes

C. SBP in participants without type 2 diabetes

hypertension and normal or near normal kidney function, all of whom were treated with either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and at least 1 additional antihypertensive drug, dapagliflozin (placebo-adjusted) reduced mean 24-hour ambulatory SBP by 4.3 mmHg.[20] A post-hoc analysis of the CREDENCE trial reported that in patients with CKD (eGFR 30-90 mL/min/1.73^2 and type 2 diabetes, with UACR 300-5000 mg/g), canagliflozin reduced SBP by 3.5 mmHg (placebo-adjusted), an effect similar in magnitude to what we observed.[21] The magnitude of blood pressure lowering effects observed in DAPA-CKD are also in keeping with results from meta-analyses of published SGLT2 inhibitor trials.[22,23] In contrast to earlier trials exclusively enrolling participants with type 2 diabetes, DAPA-CKD included participants with and without type 2 diabetes and with more advanced CKD (stages G2-G4/A2-A3) who are more likely to exhibit resistant hypertension.

The 2017 Hypertension Guidelines put forth by the American College of Cardiology (ACC) and American Heart Association (AHA) along with nine other professional organizations redefined hypertension as SBP 130-139 mmHg or DBP 80-89 mmHg (stage 1) and SBP ≥140 mmHg or SBP ≥90 mmHg (stage 2); the guidelines defined SBP 120-129 mmHg and DBP <80 mmHg as "elevated blood pressure." The guidelines highlighted the very high prevalence of hypertension in the adult population (in the US and other countries) and evidence in support of heightened risk of cardiovascular disease and mortality among persons with hypertension or elevated blood pressure relative to those with normal blood pressure.[24] Patients with CKD exhibit much higher rates of hypertension than persons with normal or near nor-

Table 2. Safety according to baseline SBP.

Outcome, n (%)	Dapagliflozin (n = 2149)	Placebo (n = 2149)	Odds ratio (95%CI)	P-interaction
SBP<120 (n = 629)	321	308		
SBP 120 to <130 (n = 807)	426	381		
SBP 130 to <140 (n = 1,094)	534	560		
SBP 140 to <150 (n = 859)	417	442		
SBP≥150 (n = 909)	451	458		
Discontinuation due to AEs				.64
SBP<120 (n = 629)	18 (5.6)	18 (5.8)	1.01 (0.51, 2.00)	
SBP 120 to <130 (n = 807)	22 (5.2)	19 (5.0)	1.06 (0.57, 2.01)	
SBP 130 to <140 (n = 1,094)	22 (4.1)	34 (6.1)	0.66 (0.38, 1.15)	
SBP 140 to <150 (n = 859)	24 (5.8)	20 (4.5)	1.22 (0.66, 2.26)	
SBP≥150 (n = 909)	32 (7.1)	32 (7.0)	1.05 (0.63, 1.76)	
Any SAEs*				.87
SBP<120 (n = 629)	82 (25.5)	93 (30.2)	0.80 (0.56, 1.14)	
SBP 120 to <130 (n = 807)	97 (22.8)	113 (29.7)	0.70 (0.51, 0.97)	
SBP 130 to <140 (n = 1,094)	157 (29.4)	180 (32.1)	0.88 (0.68, 1.14)	
SBP 140 to <150 (n = 859)	128 (30.7)	151 (34.2)	0.84 (0.63, 1.11)	
SBP≥150 (n = 909)	169 (37.5)	192 (41.9)	0.84 (0.64, 1.10)	
Volume depletion				.60
SBP<120 (n = 629)	28 (8.7)	12 (3.9)	2.36 (1.2, 4.9)	
SBP 120 to <130 (n = 807)	33 (7.7)	24 (6.3)	1.25 (0.73, 2.17)	
SBP 130 to <140 (n = 1,094)	23 (4.3)	18 (3.2)	1.36 (0.72, 2.57)	
SBP 140 to <150 (n = 859)	20 (4.8)	16 (3.6)	1.34 (0.69, 2.66)	
SBP≥150 (n = 909)	23 (5.1)	20 (4.4)	1.18 (0.64, 2.19)	
Acute kidney injury				.70
SBP<120 (n = 629)	22 (6.9)	20 (6.5)	1.06 (0.57, 2.0)	
SBP 120 to <130 (n = 807)	24 (5.6)	31 (8.1)	0.67 (0.38, 1.17)	
SBP 130 to <140 (n = 1094)	33 (6.2)	48 (8.6)	0.70 (0.44, 1.11)	
SBP 140 to <150 (n = 859)	33 (7.9)	35 (7.9)	1.0 (0.61, 1.64)	
SBP≥150 (n = 909)	43 (9.5)	54 (11.8)	0.79 (0.51, 1.20)	

* Includes death. AE, adverse event; SAE, serious adverse event; SBP, systolic blood pressure.

mal kidney function, and suffer large excess of associated complications, particularly heart failure, stroke, and arrhythmia, including sudden death.[1] While lifestyle interventions, including exercise, weight loss, and dietary modification (including salt restriction) are typically recommended for patients with and without CKD, they are rarely sufficient to bring hypertensive patients toward the "elevated" or normal blood pressure range. ACE inhibitors and ARBs (either/or) are considered first-line agents for the treatment of hypertension in the general population and are strongly recommended for patients with CKD. Particularly in patients with CKD and albuminuria or proteinuria, high-quality evidence has demonstrated ACE inhibitors and ARBs impart meaningful benefits in terms of slowing progression of CKD,[25-27] and potentially improve or preserve left ventricular function relative to other antihypertensive agents that can lower SBP and/or DBP but do not reduce the risk of progressive kidney disease or cardiovascular events.[28-31] Since randomized clinical trials have demonstrated substantial benefits of SGLT2 inhibitors in patients with CKD and albuminuria, these agents should be prescribed for reasons other than lowering blood pressure. However, use of dapagliflozin in addition to, or in place of, antihypertensive agents other than ACE inhibitors or ARBs could improve control of hypertension and provide incremental benefits, while ameliorating potential AEs, avoiding less well-tolerated antihypertensive agents or using them at lower doses than might otherwise be required.

The mechanism for blood pressure lowering effects is thought to be explained by modest natriuresis and diuresis. Several studies have reported that SGLT2 inhibitors induce transient increases in urine volume and natriuresis in patients with type 2 diabetes, accompanied by a plasma volume contraction and increases in hematocrit.[32,33] However, these studies were not performed in patients with standardized sodium intake, which would be required to reliably assess effects on natriuresis and blood pressure. In a carefully designed study during which participants were subject to standardized sodium restriction, dapagliflozin did not increase 24-hour sodium or volume excretion after 4 days or 14 days of treatment in participants with type 2 diabetes or in those with CKD without type 2 diabetes, suggesting that mechanisms other than diuresis may account for the blood pressure lowering properties of dapagliflozin.[34,35] These may include inhibition of the sympathetic nerve system or restoration of endothelial function as suggested by studies demonstrating improvements in pulse wave velocity and endothelial glycocalyx during SGLT2 inhibition.[36-38]

Figure 6. Spline curves for relationship treatment effects for primary outcome as function of baseline DBP. DBP, diastolic blood pressure.

A. DBP in the total population

B. DBP in participants with type 2 diabetes

C. DBP in participants without type 2 diabetes
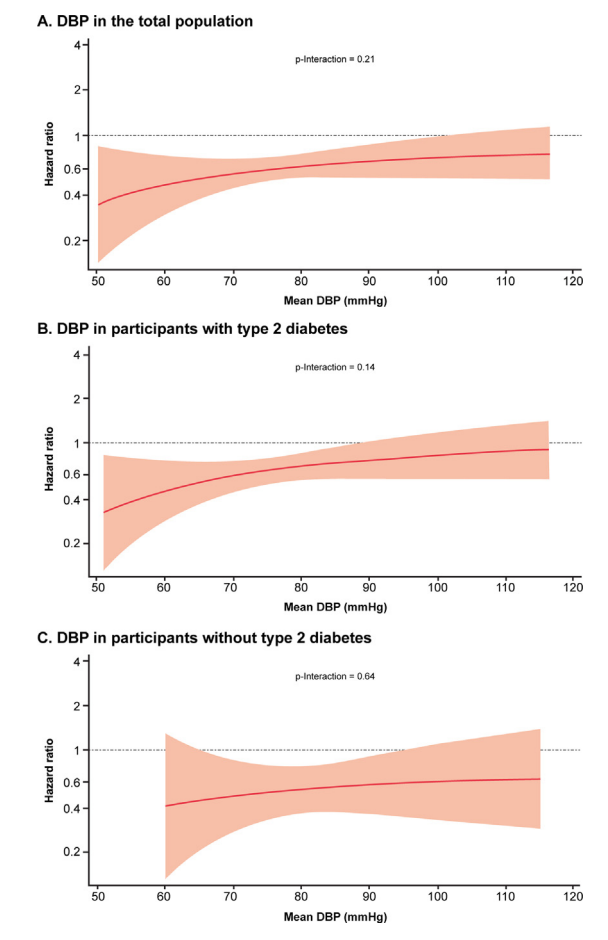
These analyses have several strengths. Data were derived from a randomized trial and major kidney and cardiovascular events were adjudicated by an independent panel. Trial participants were diverse by age, sex, country of origin, and primary cause of kidney disease. The majority of participants were on guideline-recommended therapies at baseline; nearly all participants were treated with ACE inhibitors or ARBs and other agents proven to reduce rates of cardiovascular disease. We saw modest but clinically meaningful reductions in SBP that were consistent across subgroups categorized by an array of baseline characteristics. We observed benefits of dapagliflozin on kidney and cardiovascular disease across the spectrum of baseline SBP and DBP. There are also several limitations. DAPA-CKD was not designed to determine the effects of dapagliflozin on blood pressure. As such, there were no instructions provided on recommended equipment, physical location, timing, number of repeated measurements, or other methods of blood pres-

sure determination. Other than the requirement that participants be treated with guideline recommended, maximally tolerated doses of ACE inhibitors or ARBs, the approach to hypertension management was left to the discretion of the investigators, vis-a-vis the blood pressure target and the approaches – pharmacologic and nonpharmacologic – undertaken to achieve the desired level of control. There were no specific dietary recommendations provided to trial participants. Since antihypertensive agents other than ACE inhibitors and ARBs were not consistently administered, we were unable to determine whether the antihypertensive effects of dapagliflozin were enhanced or diminished with coadministration of other agents. However, we have previously demonstrated that the kidney and cardiovascular benefits of dapagliflozin were consistently observed with and without use of several cardiovascular medications, including commonly prescribed antihypertensive classes, including beta adrenergic antagonists, calcium channel blockers, and diuretic agents.[39] Finally, we should note that the average effect of dapagliflozin on SBP falls below that observed for medications (or devices) developed for the control of hypertension; nevertheless, among patients who are receiving dapagliflozin for other approved indications, its effect on SBP may offer some incremental benefit.

In summary, among participants enrolled in the DAPA-CKD trial with and without type 2 diabetes with CKD stages G2−G4/A2−A3, dapagliflozin yielded a roughly 3 mmHg placebo-adjusted reduction in SBP. The beneficial effects of dapagliflozin on kidney and cardiovascular events were evident across the spectrum of SBP and DBP. These findings should inform clinical decisions undertaken when aiming to optimize control of hypertension in patients with CKD.

Funding

Conflict of interest

HJLH has received a grant/contract from AstraZeneca, Boehringer Ingelheim, Janssen, Novo Nordisk and has received consulting fees from AstraZeneca, Abbvie, Boehringer Ingelheim, CSL Behring, Bayer, Chinook, Dimerix, EliLilly, Gilead, Goldfinch, Merck, Novartis, NovoNordisk, Janssen, Travere Pharmaceuticals. He has received honoraria from AstraZeneca and Novo Nordisk, and travel grant from Eli-Lilly.

MP, PV, and RT report no conflicts of interest.

NJ reports travel grants from AstraZeneca.

RC-R has received support from AstraZeneca for this manuscript as being a member of the DAPA-CKD steering committee. He has received grants from AstraZeneca, GlaxoSmithKline, and Novo Nordisk; and honoraria as

CRediT authorship contribution statement

Hiddo JL Heerspink: Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Michele Provenzano:** Writing – review & editing, Validation, Formal analysis. **Priya Vart:** Writing – review & editing, Software, Formal analysis, Data curation. **Niels Jongs:** Writing – review & editing, Software, Formal analysis, Data curation. **Ricardo Correa-Rotter:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Peter Rossing:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Patrick B. Mark:** Writing – review & editing. **Roberto Pecoits-Filho:** Writing – review & editing, Validation, Methodology, Investigation. **John JV McMurray:** Writing – review & editing, Validation, Investigation, Formal analysis. **Anna Maria Langkilde:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **David C. Wheeler:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Robert B. Toto:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Glenn M. Chertow:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis.

Data availability

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

Acknowledgments

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