Hypertension

ORIGINAL ARTICLE

Cardiovascular-Kidney Effects of Dapagliflozin in Patients at Cardiovascular Risk With or Without Type 2 Diabetes: Results of a Randomized, Double-Blind, Placebo-Controlled Trial

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BACKGROUND: We investigated the impact of 12 weeks of sodium-glucose cotransporter-2 inhibition (dapagliflozin 10 mg daily) on vascular stiffness, cardiac and kidney function, and neurohormonal pathways in participants at cardiovascular risk.

METHODS: This randomized double-blind, parallel-group, placebo-controlled study enrolled 51 participants with at least 1 established cardiovascular condition or cardiovascular risk factor. Participants underwent 3 sequential assessments under clamped euglycemia (4–6 mmol/L): at baseline, at 1 week and 12 weeks of treatment. The primary outcome was vascular arterial stiffness, quantified as augmentation index and pulse-wave velocity. Secondary outcomes included: blood pressure, body fluid composition, noninvasive cardiac output monitoring, arterial vasodilatation tests, heart rate variability, echocardiography, iohexol-measured glomerular filtration rate, and natriuresis.

RESULTS: Dapagliflozin decreased vascular arterial stiffness, as measured by aortic augmentation index (placebo-adjusted change of −7.4±2.8%, P=0.01) after 12 weeks. Dapagliflozin acutely decreased extracellular fluid (−0.8±0.3 L, P=0.004), with sustained reductions in thoracic fluid content at 12 weeks (−3.3±1.5 $k\Omega^{-1}$, P=0.03). Reductions in measured glomerular filtration rate (−5.8±2.1 mL/min per 1.73m^2, P=0.008) were accompanied by acute increases in proximal sodium excretion (5.1±2.2%, P=0.03), absolute fractional distal sodium reabsorption (4.4±2.1%, P=0.04), and urine adenosine (0.21±0.08 mmol/L per µmol Cr, P=0.01).

CONCLUSIONS: Dapagliflozin induced early cardiorenal changes in individuals at varying levels of cardiovascular risk in whom evidence of clinical protection is lacking. Clinical trials in lower-risk populations, particularly in the context of primary prevention, are needed to determine whether these effects of sodium-glucose cotransporter-2 inhibition translate into improved clinical cardiorenal outcomes.

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Key Words: dapagliflozin ■ glomerular filtration rate ■ risk factors ■ sodium ■ vascular stiffness

Cardiovascular disease remains a leading global cause of morbidity and mortality[1,2] and shares a strong bidirectional relationship with kidney disease. Specifically, patients with cardiovascular disease are at 2- to 4-fold greater risk of chronic kidney disease (CKD).[3] Similarly, patients with CKD are at increased

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NOVELTY AND RELEVANCE

What Is New?

This study shows that dapagliflozin improves early cardiovascular and kidney health markers after 12 weeks in patients at varying cardiovascular risk, with or without type 2 diabetes.

What Is Relevant?

These improvements were seen in people who would not typically qualify for SGLT2 (sodium-glucose cotransporter-2) inhibitors under current guidelines. This suggests potential benefits for a wider group of patients.

Clinical/Pathophysiological Implications?

Early use of SGLT2 inhibitors may help prevent cardiovascular and kidney disease in at-risk individuals. These findings highlight the need for larger trials to assess whether earlier intervention can improve outcomes, even in those without diabetes/cardiovascular disease.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
AIx	augmentation index
ANP	atrial natriuretic peptide
ASCVD	atherosclerotic cardiovascular disease
BNP	B-type natriuretic peptide
CKD	chronic kidney disease
E/e′	left ventricular filling pressures/diastolic function
FELi	fractional excretion of lithium
FE_{Na}	fractional excretion of sodium
FMD	flow-mediated dilatation
GFR	glomerular filtration rate
PWV	pulse wave velocity
RAAS	renin-angiotensin-aldosterone system
SGLT2	sodium-glucose cotransporter 2
T2D	type 2 diabetes
TGF	tubuloglomerular feedback

risk of cardiovascular events.[4,5] SGLT2 (sodium-glucose cotransporter-2) inhibitors are highly effective in lowering adverse cardiovascular and kidney outcomes,[6,7] and are currently recommended in patients with type 2 diabetes (T2D) with or at high risk for atherosclerotic cardiovascular disease (ASCVD),[8] and in patients with heart failure and CKD regardless of T2D status.[9,10]

However, less is known about the efficacy of SGLT2 inhibition in patients with cardiovascular risk factors who do not yet meet criteria for indication, particularly in the context of primary prevention of cardiovascular and kidney events. This includes at-risk patients with estimated glomerular filtration rate (GFR) >45 mL/min per 1.73m^2, without albuminuria or heart failure, as well as patients with T2D without ASCVD or at high ASCVD risk. Analyses of kidney outcome studies demonstrate that treatment with SGLT2 inhibition earlier in the course of kidney disease is associated with a greater time to dialysis initiation.[11] Given the bidirectional association between cardiovascular and kidney risk, this highlights a potentially important gap in current treatment guidelines: individuals with cardiovascular risk factors who do not yet meet formal indications for SGLT2 inhibitor therapy may still benefit from early initiation, potentially achieving similar reductions in future cardiovascular and kidney events as those already eligible for treatment.

A large body of work has demonstrated clinical cardiovascular and kidney protection with SGLT2 inhibition. These benefits are consistent across subgroups with and without T2D, and independent of baseline glycated hemoglobin or glycated hemoglobin reductions after therapy.[12,13] Several mechanisms have been proposed to underlie the cardiovascular and kidney protective effects of SGLT2 inhibition. Among these are reductions in arterial stiffness, natriuresis, lowering of glomerular pressure, and improvements in kidney metabolic perturbations, though this has mostly been limited to cohorts with diabetes.[14–17] To date, no human studies have used an integrative approach to better understand the incremental effect of SGLT2 inhibitors on the cardiokidney-metabolic axis across the cardiovascular risk strata, including both patients with and without diabetes and beyond those currently meeting indication criteria. Moreover, in the absence of outcome data in lower-risk groups, mechanistic studies may offer insight in how these therapies could translate to novel patient populations in the future.

In the present trial, our aim was to understand the effects of SGLT2 inhibition on vascular stiffness, cardiac and kidney function, natriuresis, and neurohormonal pathways in participants at increased cardiovascular risk with or without T2D. The primary objective was to determine if dapagliflozin modifies arterial stiffness, a surrogate marker of cardiovascular risk after 12 weeks of treatment. Arterial stiffness captures the cumulative effects of hemodynamic and metabolic stress on

the vasculature and serves as a validated surrogate marker of cardiovascular risk, independently predicting future events in individuals without established end-organ disease.[18–22] Secondary objectives assessed the mechanisms associated with cardio-kidney protection, incorporating comprehensive measurements of cardiac structure and function, tubular sodium handling, volume status, and metabolic health.

MATERIALS AND METHODS

Study Participants

The data supporting the findings of this study are available from the corresponding author (D.Z.I.C.) on reasonable request. A detailed list of study inclusion and exclusion criteria assessed at screening is reported in Table S1. Briefly, the inclusion criteria were as follows: patients at increased cardiovascular risk, with an estimated GFR ($GFR_{CKD\text{-}EPI(2021)}$) ≥30 mL/min per 1.73m^2, average seated blood pressure ≤160/100 at screening, glycated hemoglobin <12.0% for patients with T2D, on a stable dose of a maximally tolerated ACE (angiotensin-converting enzyme) inhibitor, angiotensin receptor blocker, or renin inhibitor for ≥30 days before screening, on a stable diuretic dose for ≥14 days before baseline visit. Increased cardiovascular risk was defined as patients ≥50 years of age with ≥1 cardiovascular coexisting condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, CKD ≥G3, or chronic heart failure of New York Heart Association class II or III) or patients ≥60 years of age with ≥1 cardiovascular risk factor (microalbuminuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index <0.9). The local Research Ethics Board at the University Health Network (Toronto, Canada) approved the protocol and study participants gave informed consent before study procedures. The study was conducted according to the International Conference on Harmonization on Good Clinical Practice.

Study Design

This single-center, double-blind, placebo-controlled, parallel-group clinical trial was registered on January 23, 2020, with a study protocol and statistical analysis plan. Subjects at Toronto General Hospital, Canada, who passed screening completed baseline physiological assessments before undergoing 1:1 randomization to receive either 10 mg oral dapagliflozin once daily or a matched placebo. A computer-generated randomized code generated by an independent UHN biostatistician was sent directly to the pharmacy to maintain blinding of the study coordinators involved with consenting and enrolling, investigators and participants. Study medication was initiated the morning after the baseline visit, and participants returned for identical assessments at acute (week 1) and chronic (week 12) follow-up visits (Figure S1). These time points were selected to evaluate whether proximal tubular natriuresis induces an early, tubuloglomerular feedback (TGF)–mediated reduction in GFR at week 1,[14,23,24] followed by a return toward baseline by Week 12, reflecting renal function stability as observed in clinical trials. Study drug and a matching placebo were provided by AstraZeneca.

The primary outcome of this study was the change in arterial stiffness after 12 weeks of dapagliflozin treatment, assessed as a marker of vascular health and nitric oxide availability. Both short-term (1 week) and longer-term (12 weeks) effects were measured. Secondary outcomes included changes in vascular and systemic function, such as flow-mediated dilation, blood pressure (seated and supine), stroke volume, echocardiography-derived cardiac output and volume markers derived from bioimpedance spectroscopy. The study also evaluated hormone responses related to fluid balance, including natriuretic peptides and components of the renin-angiotensin-aldosterone system (RAAS). Effects on kidney function were assessed through measures of sodium handling, iohexol-measured GFR and urine adenosine.

Physiological assessments at baseline, Week 1 and Week 12 of therapy were performed during controlled clamped euglycemic conditions (4–6 mmol/L),[25] to minimize confounding influences of neurohumoral activation secondary to hyperglycemia.[25,26] A peripheral venous cannula was inserted into the left arm to facilitate the infusion of glucose and insulin. Blood glucose levels were measured using a glucose meter. If glucose values were outside the target euglycemic range of 4.0 to 6.0 mmol/L, insulin was administered at a dose calculated per kilogram of body weight or intravenous/oral dextrose was provided as appropriate. Blood glucose was subsequently monitored and adjusted with insulin or dextrose every 15 to 30 minutes until euglycemia was achieved. Once within the target range, glucose measurements were performed every 30 to 60 minutes to ensure maintenance of stable euglycemia throughout the clamp procedure.

Participants were instructed to adhere to a high-sodium (>150 mmol/d), moderate protein diet (<1.5 g/kg/d) for 7 days leading up to each of the 3 visits to ensure volume repletion and to avoid the confounding hyperfiltration effect attributable to high protein intake.[27] Participants were asked to avoid alcohol and tobacco for ≥72 hours and fast overnight ≥12 hours before all 3 visits. All measures except sitting blood pressure were captured in the supine position.

Plasma and Urine Sample Collection and Molecular Profiling

Participants collected 24-hour urine 1 day before the physiological assessment visit. On arrival and before euglycemic clamping, safety blood work, spot urine, weight and waist circumference were collected using standard laboratory methods. Glycated hemoglobin was measured by high-performance liquid chromatography.

After the euglycemic clamp was achieved but before iohexol infusion, baseline plasma, serum and urine samples were collected. Baseline plasma samples were profiled for RAAS and volume markers, including angiotensin II, aldosterone, plasma renin concentration, ACE protein, plasma renin activity, BNP (B-type natriuretic peptide), and ANP (atrial natriuretic peptide), norepinephrine, epinephrine, and urine adenosine.[14,28–31] Analytic methods are described in Supplemental Methods.

Measurement of Kidney Function at Each Physiological Assessment Visit

GFR was measured at euglycemia in the supine position by infusing iohexol (1500 mg Omnipaque) over 2 minutes through a third intravenous line, as described previously.[14] After 120

minutes of equilibration, blood samples were collected every 30 minutes up to 240 minutes postiohexol infusion. Plasma iohexol concentrations were measured[32] and extrapolated for the clearance curve.[33]

Tubular sodium handling was measured using established sodium and lithium clearance techniques[34,35] At 22:00 hours on the night before the assessments (weeks 0, 1, and 12), all participants took 300 mg of oral lithium carbonate (Li^+CO_3) to derive renal segmental tubular Na^+/Li^+ clearance measurements the following day. Blood and urine samples were obtained at 10:00h the day of the visit after clamped euglycemic conditions were achieved to measure distal and proximal tubular sodium handling. Fractional excretion of sodium (FE_{Na}), fractional excretion of lithium (FE_{Li}), and absolute distal sodium reabsorption rate (FE_{Li}—FE_{Na}) were calculated using conventional formula described previously.[36]

Measurement of Hemodynamic and Metabolic Function at Each Physiological Assessment Visit

Arterial stiffness was captured (SPC-301, Millar Instruments SphygmoCor, AtCor Medical Systems Inc., Sydney, Australia) using a high-fidelity micromanometer. The right radial and carotid artery waveforms were recorded to generate corresponding central aortic pressure waveform data. The difference between the second systolic peak and inflection point was expressed as a percentage of the central pulse pressure, indexed to a 75 bpm average heart rate, and reported as aortic augmentation index (AIx).[20–22] Carotid-femoral pulse-wave velocity (PWV) was measured by consecutive recordings of the ECG-gated right carotid and femoral artery waveform.[37] Two time domain indices of heart rate variability were also recorded for 10 minutes: root mean square successive difference and SD of normal-to-normal interval. Measurements were taken twice, and averaged.

Blood pressure was captured using 2 monitoring systems. First, an automated sphygmomanometer (DINAMAP sphygmomanometer, Critikon, FL) was used to measure seated mean arterial pressure, systolic and diastolic blood pressure, and heart rate over the right brachial artery. Second, a noninvasive cardiac output monitoring device (Cheetah Medical, Newton Center, MA, FL) was used to capture 3 consecutive blood pressure and cardiac measures (ie, cardiac output, stroke volume, systemic vascular resistance, thoracic fluid content) using ECG-based bioimpedance.[38] Measurements were replicated and averaged.

Echocardiography, using the General Electric's Vivid 7 and E9 (GE, 7–15 MHz linear array transducer, General Electric Corp, Wauwatosa, WI) ultrasound system, transthoracic 2-dimensional images, was also performed with endocardial border definition.[39] Detailed echocardiography procedure is provided in the Supplemental Methods.

Flow-mediated dilatation (FMD) was quantified, as per our previous work[40–43] using vascular ultrasonography (Vividi, 7–15 MHz linear array transducer; GE/Vingmed, Waukesha, WI, FL) as the percent change in peak vessel diameter in response to pneumatic cuff placed distal of the antecubital fossa (cuff inflation for 5 minutes at 200 mm Hg followed by deflation) and 400 µg of sublingual glyceryl trinitrate spray. Detailed FMD procedure is provided in the Supplemental Methods.

Body composition was measured noninvasively using bioimpedance spectroscopy analysis under clamped euglycemic conditions, as described elsewhere.[44] Variables captured included extracellular fluid, total body water, fat mass, and fat-free mass. Plasma volume was estimated using the Strauss equation.[45,46]

Statistical Analysis

The primary end point of this study was the change from baseline in arterial stiffness after treatment with dapagliflozin 10 mg once daily for 12 weeks compared with placebo, defined by the difference in carotid-femoral PWV during stable euglycemic conditions. The planned sample size was based on the primary arterial stiffness end point: with an expected mean baseline carotid-femoral PWV of 7.5 m/s and an SD of the change in carotid-femoral PWV of 0.8 m/s, the expected 12-week change in carotid-femoral PWV was 0.75 m/s for the SGLT2 inhibitor group (compared with the expected change of 0 m/s in the placebo group).[47] Using a sample size calculation based on a 2-sample Student *t* test assuming an alpha-level of 0.05 and 90% power, this required 25 patients per group, for a total sample size of 50 participants.

Both acute and chronic effects of therapy were evaluated on all randomized participants, thereby repeating analysis at week 1 and week 12. Linear mixed-effects models were employed to assess the primary and secondary end points with terms for treatment group, visit, and the treatment-by-visit interaction. The vector of outcomes to assess the effect of dapagliflozin incorporated the baseline outcome value. We assumed a compound symmetry covariance structure with an intention-to-treat analysis and defined participant-level random intercept to account for repeated measures within subjects. The analyses implemented a missing-at-random framework with a restricted-maximum-likelihood approach for estimation. Diagnostics plots based on the marginal and conditional residuals were assessed for overall fit. Placebo-adjusted values were defined as the difference in mean change from baseline between the dapagliflozin and placebo groups, corresponding to the treatment-by-time interaction term in the mixed-effects model. These values represent the estimated additional effect attributable to dapagliflozin compared with placebo. Subgroup analysis was performed using a 3-way interaction model incorporating treatment, visit, and diabetes. Significant tests were 2-sided and α=0.05. Nominal *P* values are reported for the secondary outcomes. Secondary outcomes were exploratory in nature and hypothesis-generating and therefore were not corrected for multiple comparisons. Frequency of adverse events, nonadherence, and drug discontinuation was tabulated. Data were analyzed using R Statistical Software (v4.4.1; R Core Team 2024).

RESULTS

Baseline Characteristics

Of the 65 individuals screened between February 2020 and 2024, 51 were enrolled and randomized to either dapagliflozin (n=26) or placebo (n=25). All 51 participants completed the study, with the primary end point

of arterial stiffness evaluated (Figure S2). Baseline characteristics are presented in the Table. At randomization, 71% of participants were male, with a mean age of 67±9 years, body mass index of 30±7 kg/m^2, estimated $GFR_{CKD\text{-}EPI(2021)}$ of 76±20 mL/min per 1.73 m^2, systolic blood pressure of 128±16 mm Hg and a median urine albumin-to-creatinine ratio of 1.7 (0.7–3.2) mg/mmol. The majority of participants (59%) were receiving statin therapy, 37% were prescribed an ACE inhibitor, 43% an angiotensin receptor blocker, and 35% a diuretic. Diuretic and RAAS inhibitor doses remained consistent throughout the treatment period. 24 participants (47%) had T2D with similar baseline characteristics to those without T2D (Table S2).

Table. Baseline Demographic and Clinical Characteristics at Randomization

	Overall (n=51)	Dapagliflozin (n=26)	Placebo (n=25)
Male	36 (71)	17 (65)	19 (75)
Age, y	67.0±9.1	65.9±8.5	68.1±9.7
Race and ethnicity			
White	29 (57)	18 (69)	11 (44)
Black	7 (14)	2 (8)	5 (20)
Asian	11 (22)	3 (12)	8 (32)
Hispanic	1 (2)	1 (4)	0 (0)
Other	3 (6)	2 (8)	1 (4)
BMI, kg/m^2	30.1±6.9	29.4±8.6	30.8±4.6
HbA1c,* %	6.3±0.9	6.4±1.1	6.2±0.7
Hemoglobin, g/L	131.5±16.1	130.3±19.8	132.8±11.2
Glucose, mmol/L	5.5±1.6	5.7±1.9	5.3±1.2
SBP, mm Hg	127.7±15.6	129.6±14.9	125.7±16.4
DBP, mm Hg	74.6±7.6	73.7±6.3	75.6±8.8
HR, bpm	69.3±12.8	67.9±12.4	70.8±13.2
MAP, mm Hg	92.6±8.8	92.4±7.6	92.7±10.0
24-hour UACR, mg/mmol	1.7 (0.7, 3.2)	1.9 (1.2, 4.2)	1.0 (0.0, 2.6)
eGFR, mL/min per 1.73 m^2	76.4±20.0	75.2±23.4	77.7±16.1
≥90	17 (33)	10 (38)	7 (28)
≥60–<90	19 (37)	4 (15)	15 (60)
≥45–<60	13 (25)	11 (42)	2 (8)
≥30–<45	2 (4)	1 (4)	1 (4)
Concomitant medication			
ACE inhibitor	19 (37)	12 (46)	7 (28)
ARB	22 (43)	8 (31)	14 (56)
Diuretic	18 (35)	11 (42)	7 (28)
Statin	30 (59)	17 (65)	13 (52)
Medical history			
Atrial fibrillation	10 (20)	6 (23)	4 (16)
CKD	8 (16)	3 (12)	5 (20)
Coronary artery disease	3 (6)	3 (12)	0 (0)
T2D	24 (47)	14 (54)	10 (40)
Dyslipidemia	19 (37)	11 (42)	8 (32)
Heart failure	15 (29)	9 (35)	6 (24)
Hypertension	30 (59)	13 (50)	17 (68)
Peripheral artery disease	1 (2)	1 (4)	0 (0)
Stroke	11 (22)	7 (27)	4 (16)

Values are n (%) or mean±SD. UACR reported as median (min, max). eGFR was estimated with the Chronic Kidney Disease Epidemiology Collaboration formula (2021). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI indicates body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure; T2D, type 2 diabetes; and UACR, urine albumin-to-creatinine ratio.

*Measured at screening not randomization.

Effects of Dapagliflozin on Arterial Stiffness

Dapagliflozin decreased aortic AIx at 12 weeks (placebo-adjusted mean±SE change of −7.4±2.8%, *P*=0.01), with no significant effect observed acutely from baseline to 1 week (−2.9±2.6%, *P*=0.27; Figure 1; Table S3). Carotid-femoral PWV remained unchanged at 1 week (−0.81±0.86 m/s, *P*=0.35) and 12 weeks (0.46±0.81 m/s, *P*=0.57).

Effects of Dapagliflozin on Hemodynamic and Cardiovascular Parameters

Dapagliflozin did not change blood pressure at 1 week or 12 weeks (Figure 2). Stroke volume, cardiac output and total peripheral resistance did not change with dapagliflozin at 1 week or 12 weeks (Table S4).

Dapagliflozin decreased left ventricular internal diameter at diastole (−0.29±0.08 cm) and systole (−0.26±0.1 cm), indexed left ventricular mass (−10.94±4.88 g/m^2) and left ventricular filling pressures/diastolic function (E/e′) (−1.6±0.7) at 1 week (*P*≤0.03 for each comparison). This reduction in left ventricular mass persisted in a sensitivity analysis that excluded participants with atrial fibrillation. However, none of these changes remained statistically significant at 12 weeks (Table S5). No other changes in echocardiographic measures were observed after 1 week or 12 weeks of dapagliflozin (Table S5).

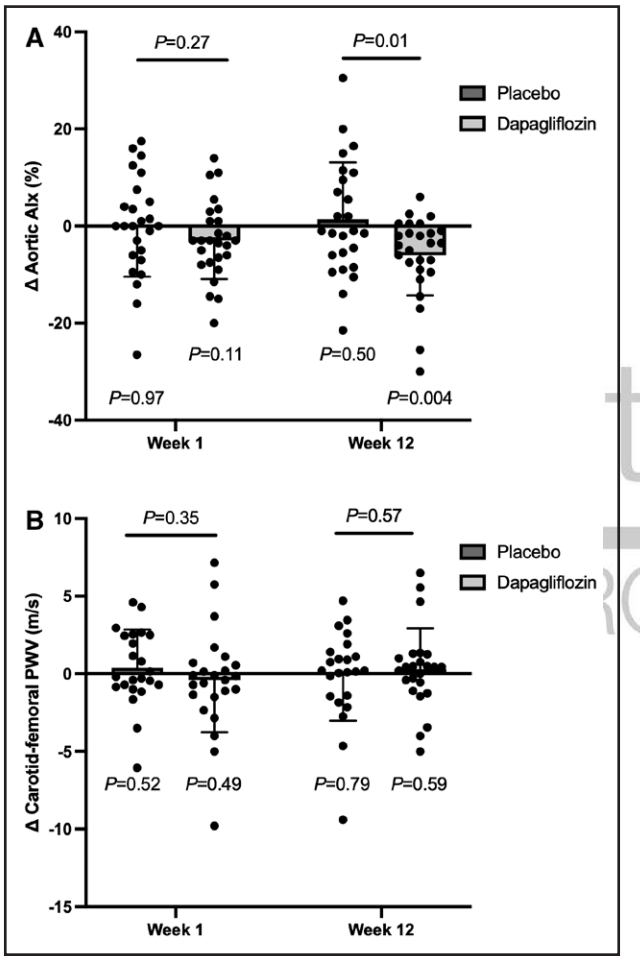

Figure 1. Changes in arterial stiffness measures after 1 week and 12 weeks of treatment.
Changes in (**A**) aortic augmentation index (AIx) and (**B**) carotid-femoral pulse-wave velocity (PWV) are reported after week 1 and week 12 of dapagliflozin treatment or placebo, subtracted from baseline values in patients at cardiovascular risk. *P* values displayed at the top of the figure correspond to between-group comparisons. All other *P* values represent within-group comparisons. A linear mixed-effects model was used to analyze end points, incorporating treatment group, visit, and treatment-by-visit interaction as fixed effects, with a patient-level intercept included as a random effect to account for within-subject correlation. Two-sided significance tests were conducted with α=0.05, and nominal *P* values were reported.

Effects of Dapagliflozin on Kidney Tubular Handling

Total glucose excretion was significantly increased in the dapagliflozin group compared with placebo by 199±27 mmol/d (*P*<0.001) after 1 week, and levels were sustained after 12 weeks of treatment (*P*<0.001; Table S6).

Dapagliflozin increased proximal sodium excretion from baseline after 1 week of treatment, as measured by the change in exogenous lithium clearance, compared with placebo (placebo-adjusted FE_{Li}: Δ5.1±2.2%, *P*=0.03; Figure 3). Dapagliflozin also acutely increased absolute fractional distal sodium reabsorption (FE_{Na}—FE_{Li}) compared with placebo (4.4±2.1%, *P*=0.04). After 12 weeks of treatment, the placebo-adjusted changes in FE_{Li} (*P*=0.31) and distal sodium handling (*P*=0.35) did not persist (Table S7). There was no effect of dapagliflozin compared with placebo on FE_{Na} from baseline to 1 week or 12 weeks. Acute proximal natriuresis was accompanied by an acute increase in 24-hour urine volume with dapagliflozin compared with placebo (*P*=0.04), but this effect was no longer significant at 12 weeks (Table S7).

The placebo-adjusted increase in urine adenosine was significant with dapagliflozin from baseline to 1 week of treatment (*P*=0.01; Table S8).

Effects of Dapagliflozin on Kidney Function

Compared with placebo, dapagliflozin decreased iohexol-measured GFR by 4.8±1.7 mL/min per 1.73m^2 (*P*=0.006) from baseline to 1 week (Figure 4). Specifically, dapagliflozin decreased measured GFR by 5.5±1.2 mL/min per 1.73m^2 (within-group: 60±3–54±3 mL/min per 1.73m^2; $P_{within\ group}$<0.001; Table S9). This acute dip in measured GFR was mirrored by the placebo-adjusted acute dip in estimated GFR by 4.8±2.0 mL/min per 1.73m^2 (*P*=0.02). The reduction

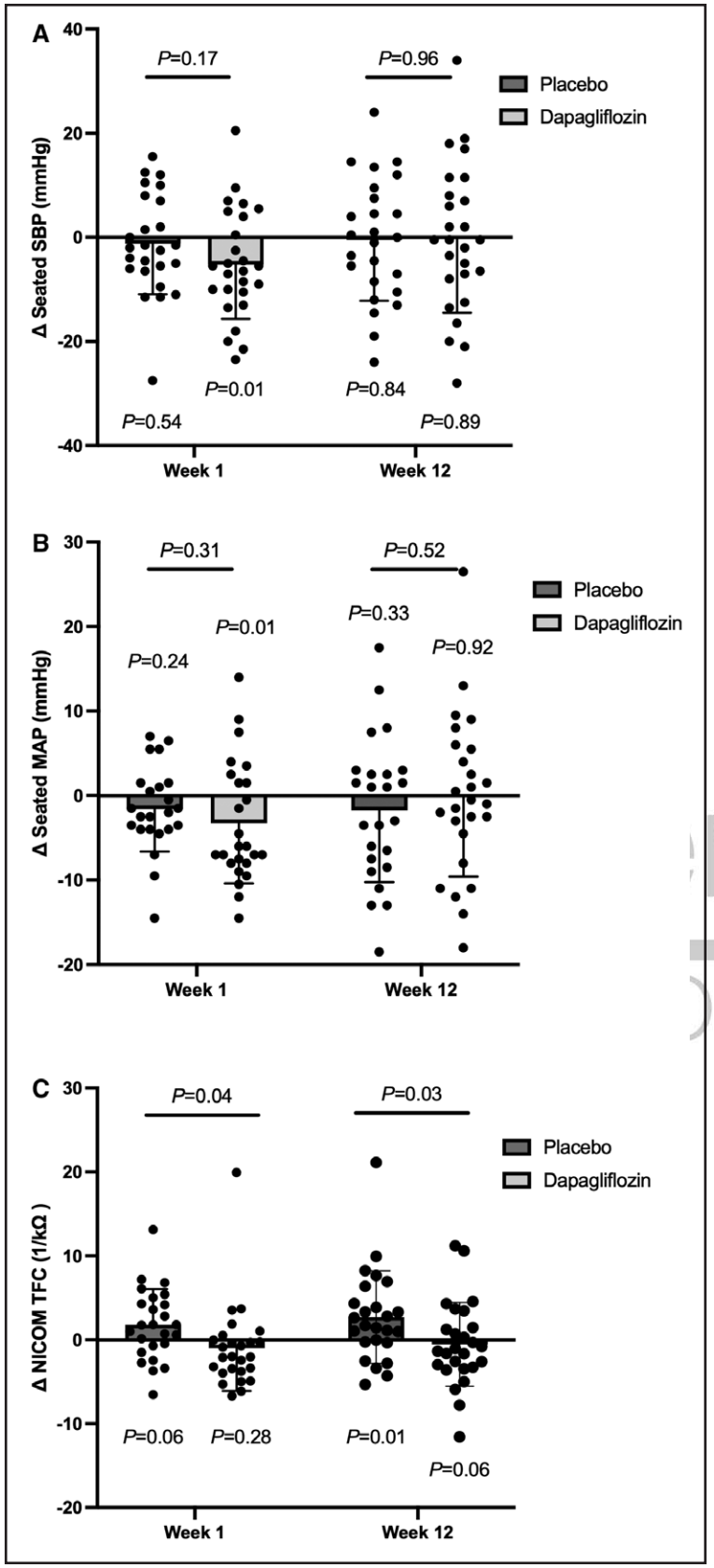

Figure 2. Changes in seated blood pressure and supine noninvasive cardiac output monitoring (NICOM) measures after 1 week and 12 weeks of treatment.

Changes in (**A**) clinical measure of systolic blood pressure (SBP), (**B**) clinical measure of mean arterial pressure (MAP), and (**C**) thoracic fluid content (TFC) by NICOM are reported after week 1 and week 12 of dapagliflozin treatment or placebo, subtracted from baseline values. *P* values displayed at the top of the figure correspond to between-group comparisons. All other *P* values represent within-group comparisons. A linear mixed-effects model was used to analyze end points, incorporating treatment group, visit, and treatment-by-visit interaction as fixed effects, with a patient-level intercept included as a random effect to account for within-subject correlation. Two-sided significance tests were conducted with α=0.05, and nominal *P* values were reported.

in measured GFR was sustained with dapagliflozin treatment compared with placebo (5.8±2.1 mL/min per 1.73m^2, *P*=0.008). Placebo-corrected changes in urine albumin-to-creatinine ratio from spot collection and protein excretion measured using 24-hour urine were not significant (Table S9).

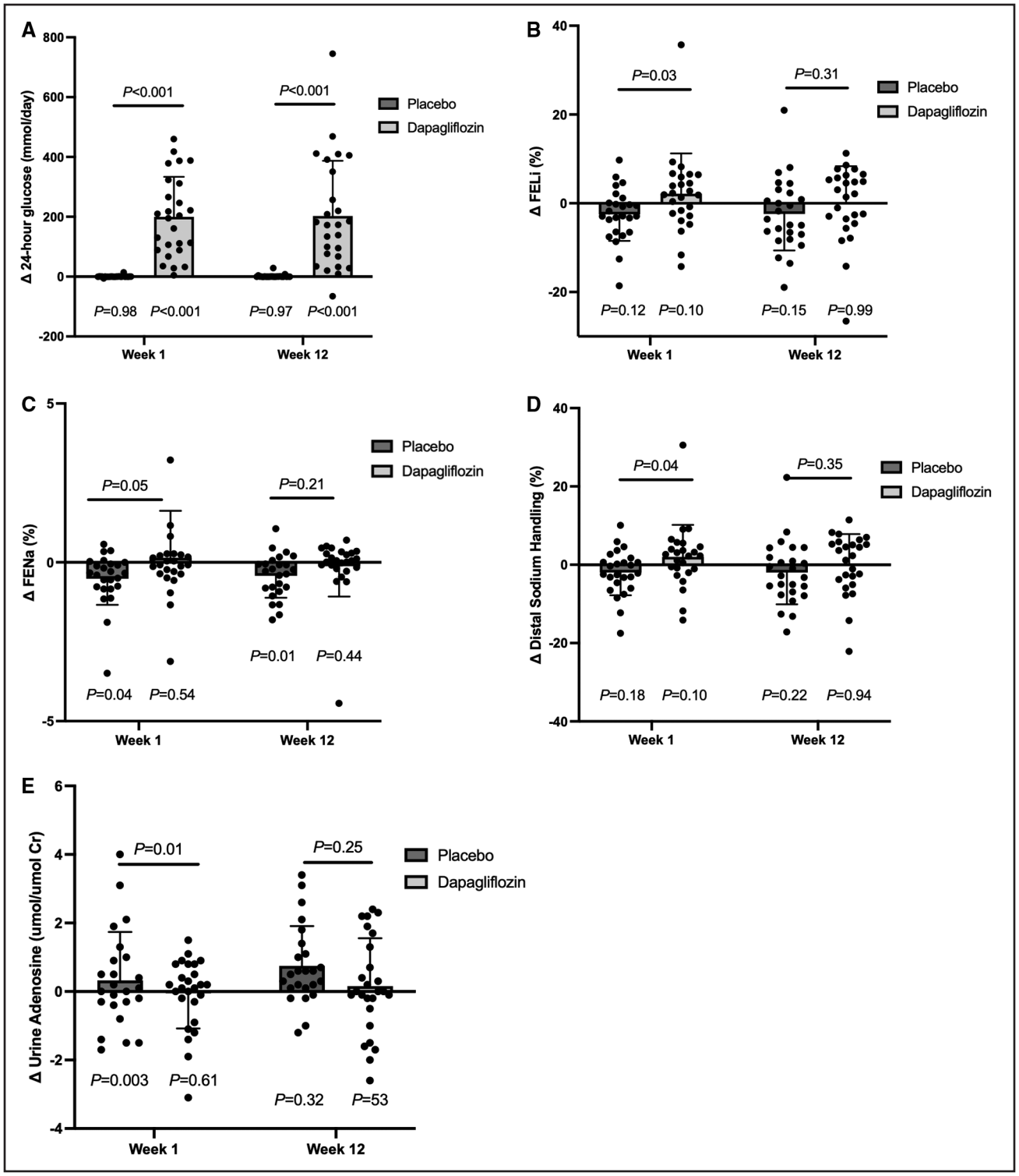

Figure 3. Acute and chronic changes in kidney tubular handling after 1 week and 12 weeks of treatment.
Changes in (**A**) 24-hour urine glucose, (**B**) fractional excretion of lithium (FE_{Li}), (**C**) fractional excretion of sodium (FE_{Na}), (**D**) distal sodium handling (FE_{Li}—FE_{Na}) and (**E**) urine adenosine normalized to creatinine, are reported after week 1 and week 12 of dapagliflozin treatment or placebo subtracted from baseline values in patients at cardiovascular risk. *P* values displayed at the top of the figure correspond to between-group comparisons. All other *P* values represent within-group comparisons. A linear mixed-effects model was used to analyze end points, incorporating treatment group, visit, and treatment-by-visit interaction as fixed effects, with a patient-level intercept included as a random effect to account for within-subject correlation. Two-sided significance tests were conducted with α=0.05, and nominal *P* values were reported.

Relationship Between Glucose Excretion, Natriuresis and GFR

Among participants treated with dapagliflozin, acute and chronic changes in total glucose excretion were not associated with changes in proximal natriuresis (Figure S3A). Changes in proximal natriuresis were not associated with the changes to iohexol-measured GFR after dapagliflozin therapy (Figure S3B).

Effects of Dapagliflozin on Plasma Volume and Body Composition

Compared with placebo, dapagliflozin treatment decreased body mass index by 0.3±0.2 kg/m^2 (P=0.04) at 1 week, but this was not sustained after 12 weeks. The initial reduction in weight with dapagliflozin by 1.0±0.4 kg (P=0.02) was sustained after chronic treatment (−1.3±0.5 kg, $P_{within\ group}$=0.01), but was not significantly different compared with placebo (Figure 5). Acute dapagliflozin treatment decreased total body water compared with placebo by 1.6±0.8 L (P=0.046; Table S10). These acute reductions in fluid content were accompanied by a placebo-adjusted reduction in fat-free mass by 2.2±1.0 kg (P=0.05) and extracellular fluid by 0.8±0.3 L (P=0.004) after 1 week of treatment. These reductions were not sustained after 12 weeks of treatment (Figure 5). Compared with placebo, 12 weeks of dapagliflozin treatment significantly decreased estimated plasma volume by 5.6±2.4% (P=0.02). Fat mass did not change with dapagliflozin after 1 or 12 weeks of treatment (Table S10). Acute placebo-adjusted reductions of 2.8±1.3 1/kΩ (P=0.04) in supine thoracic fluid content were observed with dapagliflozin compared with placebo during noninvasive cardiac output monitoring. The placebo-adjusted reductions in supine thoracic fluid content with dapagliflozin were still persistent after 12 weeks (−3.3±1.5 1/kΩ, P=0.03).

Effects of Dapagliflozin on Flow-Mediated and Glyceryl Trinitrate-Dependent Dilatation

Compared with placebo, dapagliflozin treatment was not associated with a relative change in peak instantaneous flow after cuff deflation (P=0.46; Table S11). Other measures of endothelial-dependent and endothelial-independent vascular function did not change (Table S11).

Effects of Dapagliflozin on Neurohormonal Variables and Heart Rate Variation

Compared with placebo, dapagliflozin increased plasma levels of aldosterone (103.2±31.2 pmol//L), renin (111.9±48.5 ng/L), and plasma renin activity (6.0±2.4 ng/mL per hour) at 1, but not at 12 weeks. Placebo-corrected increases in plasma angiotensinogen were only significant at 12 weeks. Urine ACE2 activity acutely increased by 76.9±12.0 µg/µmol Cr (P<0.001); this increase was sustained at 12 weeks (Table S8). Placebo-corrected increases in urine angiotensin II levels were only significant acutely (P=0.005).

Dapagliflozin did not change urinary levels of other neurohormones or natriuretic modulators. Plasma norepinephrine and epinephrine concentrations did not differ significantly between those allocated dapagliflozin or placebo, at either 1- or the 12-week session; nor did heart rate, root mean square successive difference or SD of normal-to-normal interval (Table S4; Table S8).

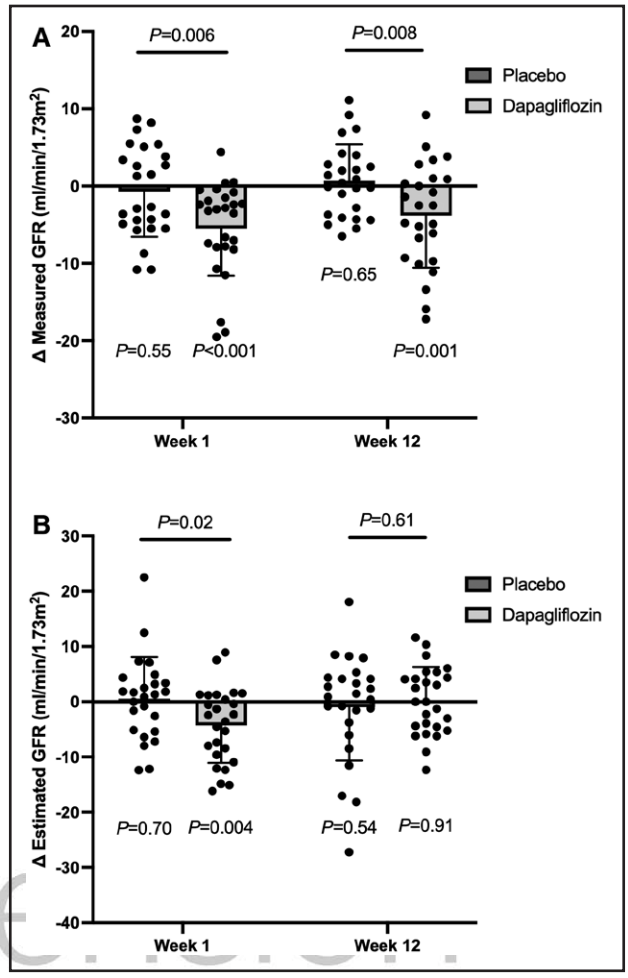

Figure 4. Changes in glomerular filtration rate after 1 week and 12 weeks of treatment.
Changes in (**A**) iohexol-measured glomerular filtration rate (GFR) and (**B**) estimated GFR by the Chronic Kidney Disease Epidemiology Collaboration 2021 equation are reported after week 1 and week 12 of dapagliflozin treatment or placebo, subtracted from baseline values in patients at cardiovascular risk. P values displayed at the top of the figure correspond to between-group comparisons. All other P values represent within-group comparisons. A linear mixed-effects model was used to analyze end points, incorporating treatment group, visit, and treatment-by-visit interaction as fixed effects, with a patient-level intercept included as a random effect to account for within-subject correlation. Two-sided significance tests were conducted with α=0.05, and nominal P values were reported.

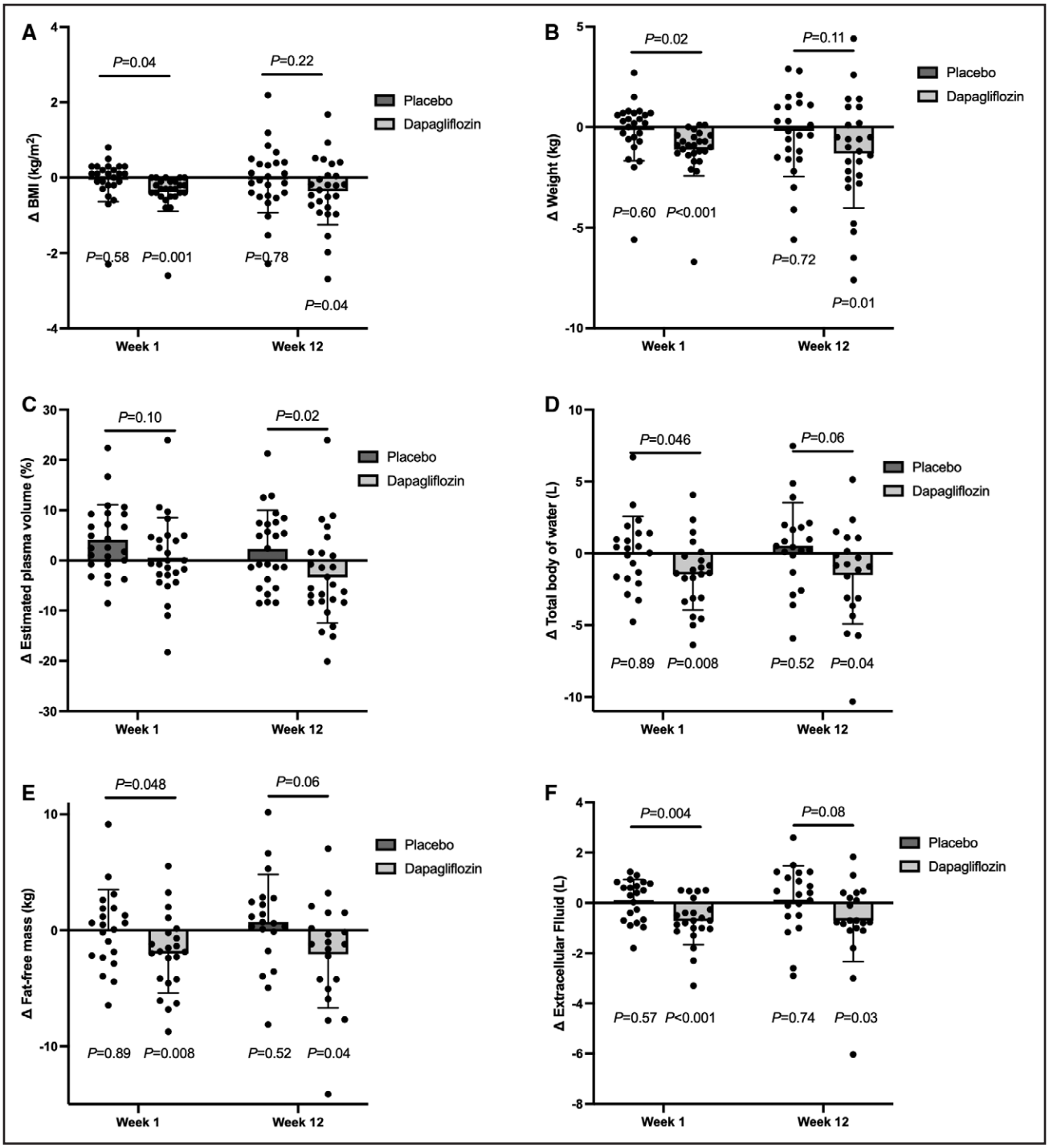

Figure 5. Changes in fluid volume and body composition after 1 week and 12 weeks of treatment.
Changes in (**A**) body mass index (BMI), (**B**) weight, (**C**) estimated plasma volume calculated by Strauss estimation, (**D**) total body of water, (**E**) fat-free mass, and (**F**) extracellular fluid are reported after week 1 and week 12 of dapagliflozin treatment or placebo subtracted from baseline values in patients at cardiovascular risk. *P* values displayed at the top of the figure correspond to between-group comparisons. All other *P* values represent within-group comparisons. A linear mixed-effects model was used to analyze end points, incorporating treatment group, visit, and treatment-by-visit interaction as fixed effects, with a patient-level intercept included as a random effect to account for within-subject correlation. Two-sided significance tests were conducted with α=0.05, and nominal *P* values were reported.

Effect of Dapagliflozin on Plasma and Urine Biochemistry

Acute dapagliflozin treatment significantly decreased plasma levels of urate by 46.0±13.5 µmol/L (*P*=0.001) from baseline and this effect was sustained with chronic treatment (*P*=0.01). Placebo-corrected changes in hemoglobin (*P*=0.09) and hematocrit (0.19), were not significant at 1 week, but did reach significance after 12 weeks of treatment (*P*=0.02 for both). Levels of magnesium

increased significantly by 0.04±0.01 mmol/L after 1 week of dapagliflozin (P=0.006), but changes were not sustained. Although no acute change in fasting plasma glucose was observed, 12 weeks of dapagliflozin led to significant reductions by −0.9±0.4 mmol/L (P=0.04). Other safety plasma and urine markers are reported in the Tables S6 and S12.

Subgroup Analysis By Diabetes Status

The effects of dapagliflozin on blood pressure, arterial stiffness (Figure S4), natriuresis, measured GFR, noninvasive cardiac output monitoring, FMD, and safety outcomes did not differ based on diabetes status.

Adverse Events

One participant assigned to the placebo group experienced a serious adverse event and required hospitalization due to heart failure. Of the adverse events of interest, 3 separate mild hypoglycemic episodes were reported, 2 of which occurred in participants randomized to dapagliflozin treatment and 1 in the placebo group. Two separate mild cases of acute kidney injury were reported during the trial, 1 in the dapagliflozin group and 1 in the placebo group. One participant randomized to the placebo group experienced a urinary tract infection that was resolved during the trial. There were no episodes of ketoacidosis or volume depletion events.

DISCUSSION

The present trial systematically explored the effects of SGLT2 inhibition on vascular, cardiac, kidney and neurohormonal variables in a mixed cohort of participants with and without T2D at varying degrees of increased cardiovascular risk. Specifically, vascular stiffness as measured by aortic AIx was reduced over 12 weeks. We also observed acute reductions in measured GFR and acute proximal tubular natriuresis—findings consistent with reductions in glomerular hypertension and hyperfiltration. Systemically, there was evidence of acute and chronic changes in volume status with the use of dapagliflozin. Dapagliflozin elicited early physiological changes relevant to cardiovascular and kidney risk, including a reduction in arterial stiffness suggestive of improved ventricular-vascular coupling, and kidney findings indicative of an intact adaptive response to changes in sodium and volume balance. These findings provide mechanistic support for the potential preventive benefits of SGLT2 inhibition in participants at varying levels of cardiovascular risk in whom evidence of clinical protection is lacking.

The present trial provides a detailed integrative analysis of SGLT2 inhibition in a patient population with and without T2D. Clinical cardiovascular and kidney benefits with SGLT2 inhibitors have been established in patients regardless of T2D status, specifically in those with CKD or heart failure.[7] Therefore, the impact of SGLT2 inhibition in this trial population is important due to its consistency with clinical benefits in people with and without T2D.[14,15,48] However, this trial extends our understanding of how SGLT2 inhibitors may provide protection in a patient population in which we do not currently have clinical trials demonstrating cardiovascular or kidney benefits. Reviewing our cohort, 15 participants without T2D and 13 participants with T2D, together representing 55% of the combined cohort, did not have a strong clinical indication for cardiovascular or kidney protection with an SGLT2 inhibitor based on current trials and guidelines. Among those without T2D were patients with an estimated GFR >45 mL/min per 1.73m^2, and without albuminuria or heart failure. Similarly, the 13 participants with T2D included individuals with an estimated GFR >45 mL/min per 1.73m^2, and without albuminuria, heart failure or established ASCVD. The mean estimated 10-year risk of ASCVD in these patients with T2D, based on the American Heart Association's Predicting Risk of Cardiovascular Disease Events score, was 9.5%. Therefore, these participants were mostly at the lower end of the cardiovascular (and kidney disease) risk spectrum. Taken together, the demonstration of cardiorenal effect with SGLT2 inhibition in patients who draw from lower cardiovascular and kidney risk populations in which evidence of cardiovascular and kidney protection is lacking strengthens the argument for large, pragmatic clinical trials or the generation of real-world evidence in this patient population.

At baseline, the aortic AIx for the cohort averaged 19%, which decreased to ≈13% after 12 weeks of dapagliflozin treatment, moving closer to, but still above, the normative value of ≈10.3% reported in 60- to 69-year-old men.[49] This reduction of about 6% to 7% may have clinical implications. Supporting this, modest increases in AIx have been linked to worse outcomes: in a meta-analysis of 5648 subjects followed for 45 months, every 10% absolute increase in central AIx was associated with a 32% higher risk of future cardiovascular events and 38% higher risk of all-cause mortality.[50] Likewise, in a cohort of patients with coronary artery disease, every 10% increase in AIx was associated with a 28% higher risk of major adverse cardiovascular events.[51] In another study, men in the highest tertile of AIx had 1.60-fold higher risk of combined cardiovascular events compared with those in the lowest tertile.[52] Taken together, these findings suggest that even modest improvements in AIx as observed in our cohort may translate to substantial cardiovascular benefit.

Carotid-femoral PWV, however, remained unchanged. The aortic AIx and carotid-femoral PWV are both generally considered indices of large artery central stiffness that provide complementary information towards patient risk.[53] For example, both the aortic AIx and

carotid-femoral PWV are independently associated with adverse events across a range of cardiovascular and kidney disease conditions.[18,19] In some populations, aortic AIx is predictive of mortality even in the setting of normal PWV.[54] However, both indices can be experimentally modified independently.[55,56] While the current work is unable to determine why dapagliflozin selectively lowered aortic AIx and not carotid-femoral PWV, 1 possibility may relate to the greater influence of arteriolar tone on aortic AIx.[56] However, reductions in AIx were not accompanied by reductions in peripheral resistance and blood pressure in our study, making it less likely that altered vasomotor tone was the primary driver. No significant changes were observed in FMD or glyceryl trinitrate, indicating that improvements in endothelial function or smooth muscle responsiveness are unlikely to account for the selective reduction in AIx. This strengthens the interpretation that changes in AIx may reflect alterations in wave reflection or peripheral arterial tone independent of conduit artery endothelial function. Consistent with this, a meta-analysis of SGLT2 inhibitors demonstrated modest improvements in FMD (standardized effect size 0.18) but no significant effect on PWV,[57] suggesting that endothelial improvements may accompany but do not necessarily drive changes in central arterial stiffness or wave reflection. Experimental evidence further supports the independent modulation of AIx and carotid-femoral PWV; administration of vasodilators such as nitroglycerin and vasoconstrictors like angiotensin II produces large shifts in AIx with minimal changes in carotid-femoral PWV in healthy subjects, highlighting greater sensitivity of AIx to peripheral vascular tone.[56] Collectively, these findings suggest that AIx reduction with dapagliflozin may preferentially reflect effects on wave reflections or small artery function rather than changes in large artery stiffness.

Dapagliflozin increased proximal and total natriuresis, as measured by FE_{Li} and FE_{Na}, respectively. This was also accompanied by increases in 24-hour glucose excretion. However, natriuresis was not sustained at 12 weeks, suggesting that adaptive mechanisms may have blunted this effect over time. This attenuation is consistent with prior findings that show the natriuretic response to SGLT2 inhibitors is most pronounced early in therapy—often evident by day 1—and diminishes with continued use following 14 days of treatment.[58] Mechanistically, this attenuated total natriuresis may be attributed to a series of counter-regulatory adaptations in tubular sodium handling, including reductions in proximal sodium excretion and increases in distal sodium reabsorption.[59–61] Proteomic studies have further implicated factors such as carbonic anhydrase and uromodulin in mediating increased sodium retention in both the proximal tubule and the thick ascending limb of Henle's loop.[59] In addition, volume contraction associated with initial natriuresis can activate the RAAS, promoting sodium reabsorption in the distal nephron.[62,63] As observed in longer-term studies (eg, 4–6 weeks), sodium excretion and FENa often return to baseline, indicating that the natriuretic effect of SGLT2 inhibition may be transient.[60,64,65] Although SGLT2 inhibition offers clinically meaningful benefits in the setting of heart failure, it is unclear to what extent, if any, these benefits are mediated by the diuretic effects of SGLT2 inhibitors.[58] Prior work initially proposed that the natriuretic and diuretic effects of SGLT2 inhibition were the primary mechanisms responsible for clinical benefit, particularly in the setting of heart failure.[66–68] However, contemporary work has suggested that these mechanisms do not mediate clinical benefit,[69,70] but serve to restore sodium balance, thereby blunting the initial natriuretic effect despite continued glucosuria. Natriuresis and diuresis appear to characterize early effects of SGLT2 inhibition that subsequently attenuate with time, suggesting activation of alternate pathways that confer clinical benefit. It has also been proposed that a persistent effect of SGLT2 inhibition on proximal tubular natriuresis resets volume homeostasis which may allow individuals to better manage episodes of volume expansion, preventing exacerbations of heart failure in those at risk.

Our results also demonstrate evidence of TGF activation within a cohort with 80% background use of renin-angiotensin blockade and 35% background use of diuretic therapy. In addition to the observed acute proximal tubular natriuresis with dapagliflozin, there was an accompanying acute and chronic dip in measured GFR as well as increases in urine adenosine. SGLT2 inhibition is known to result in an acute and reversible 4 to 6 mL/min per 1.73m^2 dip in GFR, though the exact hemodynamic mechanism that is responsible remains controversial. Glomerular perfusion is regulated via different feedback mechanisms, including distal sodium delivery to the macula densa. Sodium from the tubular lumen enters the macula densa through $Na^+/K^+/2Cl^-$ cotransporters and stimulates the local generation of ATP or adenosine.[71] By increasing distal sodium delivery, SGLT2 inhibitors are hypothesized to restore TGF and have been demonstrated to reduce calculated intraglomerular pressure.[14] Observed increases in placebo-adjusted urine adenosine with dapagliflozin suggest activation of TGF mechanisms, as early as 1 week after initiation of therapy, results that are consistent with mechanistic studies in a variety of patient populations.[42,72–74]

Acute increases in natriuresis with dapagliflozin were accompanied by acute changes in volume status. This included in significant acute reduction in extracellular fluid volume and total body water. Although natriuresis was not sustained with dapagliflozin, there was evidence of sustained volume effect with reductions in estimated plasma volume at 12 weeks. As with other findings in this study, volume effects observed in our study are consistent with existing literature. The EMPIRE-HF trial examined

the change in extracellular volume in patients with heart failure randomized to empagliflozin versus placebo for 12 weeks,[75] and showed that empagliflozin reduced estimated extracellular volume compared with placebo by a modest 0.12 L. Other studies also examined changes in extracellular volume with SGLT2 inhibition using bioimpedance spectroscopy and demonstrated reductions ranging from 0.5 to 1 L that tended to dissipate over time.[61] In contrast with this previous work, plasma volume in the current study was estimated using the Strauss equation, which evaluates changes in hematocrit relative to hemoglobin, both of which increased with dapagliflozin over time in our study.[45] Analyses of SGLT2 inhibitor outcome trials have identified changes in hematocrit to be most closely associated with improvements in cardiovascular and kidney outcomes, possibly by protection against the development of volume overload.[76–79] One major limitation of using the Strauss equation to estimate plasma volume in the context of SGLT2 inhibitors is the potential effects of this class of drugs on erythropoietin and reticulocytosis.[80,81] Regardless, changes in estimated plasma volume, bioimpedance measured extracellular fluid, and body weight observed in this study were all concordant and suggestive of systemic volume reduction, although these changes were not accompanied by sympathetic activation. Also consistent with a systemic volume effect was the demonstration of acute RAAS activation—effects that have been mirrored in previous work.[16]

There are limitations to this analysis. First, although acute measured GFR changes were noted, we did not assess renal blood flow in this study. In the absence of renal hemodynamic measurements, we were unable to discern whether changes in postglomerular arteriolar resistance or preglomerular arteriolar resistance contributed to GFR changes. Second, treatment allocation was not stratified by diabetes status, which may limit the ability to draw definitive conclusions about differential treatment effects between participants with and without diabetes. A third limitation is multiple comparisons between groups, which could increase the risk of type 1 errors. Fourth, discordant response observed between aortic AIx and carotid-femoral PWV complicates interpretation, especially given that PWV generally demonstrates greater reproducibility and validity compared with AIx. Finally, despite intentional efforts to recruit female participants, the study population was predominantly male. This limitation reflects a broader challenge, as females are generally underrepresented in clinical trials.[82]

In conclusion, in individuals at varying levels of cardiovascular risk, dapagliflozin treatment over 12 weeks led to measurable improvements in vascular function, volume status, glycemic control, and renal sodium handling—consistent with mechanisms thought to underlie long-term cardiovascular and kidney protection. Reductions in AIx are suggestive of improved ventricular-vascular coupling with dapagliflozin, which, along with changes in volume status and restoration of TGF, leading to kidney protection, may reduce the risk of heart failure with preserved ejection fraction in this cohort. These cardiorenal effects may represent early signals relevant to the prevention of cardiovascular complications in this at-risk population. This study suggests that SGLT2 inhibitors may benefit a broader population at varying cardiovascular risk, beyond those currently approved, and can inform future trials aimed at identifying underserved cardiovascular risk subgroups who may also benefit from earlier intervention. Longer-term clinical trials, especially in patients at lower cardiovascular risk from the perspective of primary prevention, are required to assess if these effects translate to improvements in clinical cardio-kidney outcomes.

PERSPECTIVES

This study offers mechanistic insight into how SGLT2 inhibition may confer cardiovascular and kidney protection, even among individuals at lower cardiorenal risk who fall outside current treatment indications. By demonstrating favorable changes in vascular stiffness, glomerular hemodynamics, and systemic volume regulation, the findings support a broader physiological role for SGLT2 inhibitors in modulating risk pathways early in disease progression. These observations raise the possibility that SGLT2 inhibitors could be effective in the primary prevention of cardiovascular and kidney complications, particularly in patients with subclinical risk profiles. Importantly, the concordance between vascular, renal, and volume markers despite the absence of overt clinical disease underscores the potential utility of early intervention in modifying disease trajectories. This integrative approach highlights a need for future trials that move beyond traditional high-risk populations and instead focus on pragmatic strategies to identify and treat individuals earlier in the course of disease. Although the current findings are hypothesis-generating, they suggest that SGLT2 inhibitors could be considered in a broader array of clinical contexts. Further long-term studies and real-world evidence are warranted to determine whether these early physiological effects translate into meaningful reductions in hard cardiovascular and kidney end points in diverse, lower-risk populations.

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Supplemental Material

Supplemental Methods
Tables S1–S12
Figures S1–S4

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