

Urinary Sodium and Potassium Excretion and Risk of Cardiovascular Events

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THERE IS UNCERTAINTY REGARDING the optimal daily intake of sodium, which confers most protection against the risk of cardiovascular (CV) disease.¹ The World Health Organization² recommends a sodium intake of less than 2 g per day, a level that is largely based on projections made from relatively small and short-term clinical trials evaluating the effects of sodium restriction on blood pressure in primary prevention populations.³ However, findings from prospective cohort studies, evaluating the association between sodium intake and CV events, have been conflicting.¹ For example, although some have reported a positive association between sodium intake and CV mortality,⁴⁻⁷ others have not,⁸⁻¹¹ and some have reported an inverse association.^{12,13} In particular, a re-

Context The precise relationship between sodium and potassium intake and cardiovascular (CV) risk remains uncertain, especially in patients with CV disease.

Objective To determine the association between estimated urinary sodium and potassium excretion (surrogates for intake) and CV events in patients with established CV disease or diabetes mellitus.

Design, Setting, and Patients Observational analyses of 2 cohorts (N=28 880) included in the ONTARGET and TRANSCEND trials (November 2001-March 2008 from initial recruitment to final follow-up). We estimated 24-hour urinary sodium and potassium excretion from a morning fasting urine sample (Kawasaki formula). We used restricted cubic spline plots to describe the association between sodium and potassium excretion and CV events and mortality, and to identify reference categories for sodium and potassium excretion. We used Cox proportional hazards multivariable models to determine the association of urinary sodium and potassium with CV events and mortality.

Main Outcome Measures CV death, myocardial infarction (MI), stroke, and hospitalization for congestive heart failure (CHF).

Results At baseline, the mean (SD) estimated 24-hour excretion for sodium was 4.77 g (1.61); and for potassium was 2.19 g (0.57). After a median follow-up of 56 months, the composite outcome occurred in 4729 (16.4%) participants, including 2057 CV deaths, 1412 with MI, 1282 with stroke, and 1213 with hospitalization for CHF. Compared with the reference group with estimated baseline sodium excretion of 4 to 5.99 g per day (n=14 156; 6.3% participants with CV death, 4.6% with MI, 4.2% with stroke, and 3.8% admitted to hospital with CHF), higher baseline sodium excretion was associated with an increased risk of CV death (9.7% for 7-8 g/day; hazard ratio [HR], 1.53; 95% CI, 1.26-1.86; and 11.2% for >8 g/day; HR, 1.66; 95% CI, 1.31-2.10), MI (6.8%; HR, 1.48; 95% CI, 1.11-1.98 for >8 g/day), stroke (6.6%; HR, 1.48; 95% CI, 1.09-2.01 for >8 g/day), and hospitalization for CHF (6.5%; HR, 1.51; 1.12-2.05 for >8 g/day). Lower sodium excretion was associated with an increased risk of CV death (8.6%; HR, 1.19; 95% CI, 1.02-1.39 for 2-2.99 g/day; 10.6%; HR, 1.37; 95% CI, 1.09-1.73 for <2 g/day), and hospitalization for CHF (5.2%; HR, 1.23; 95% CI, 1.01-1.49 for 2-2.99 g/day) on multivariable analysis. Compared with an estimated potassium excretion of less than 1.5 g per day (n=2194; 6.2% with stroke), higher potassium excretion was associated with a reduced risk of stroke (4.7% [HR, 0.77; 95% CI, 0.63-0.94] for 1.5-1.99 g/day; 4.3% [HR, 0.73; 95% CI, 0.59-0.90] for 2-2.49 g/day; 3.9% [HR, 0.71; 95% CI, 0.56-0.91] for 2.5-3 g/day; and 3.5% [HR, 0.68; 95% CI, 0.49-0.92] for >3 g/day) on multivariable analysis.

Conclusions The association between estimated sodium excretion and CV events was J-shaped. Compared with baseline sodium excretion of 4 to 5.99 g per day, sodium excretion of greater than 7 g per day was associated with an increased risk of all CV events, and a sodium excretion of less than 3 g per day was associated with increased risk of CV mortality and hospitalization for CHF. Higher estimated potassium excretion was associated with a reduced risk of stroke.

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cent study¹³ has rekindled the controversy by reporting an increased risk in CV mortality at low sodium intake levels that are recommended by many current guidelines. Clarifying the optimal daily intake of sodium is particularly important in patients with established CV disease, where it has been inadequately studied. Patients with CV disease may be especially vulnerable to the CV effects of high and low sodium intake and are most likely to receive recommendations on restricting sodium intake.

Epidemiological studies have also reported that increased potassium intake is associated with reduced risk of CV disease, most notably for stroke,¹⁴ although the optimal level of daily potassium intake has not been established. Potassium intake is also a proposed modifier of the association between sodium intake and CV disease.¹⁵

We determined the association between sodium and potassium excretion (as measures of intake) and CV events and mortality in a cohort of 29 000 high-risk patients, using calculated estimates of 24-hour urinary sodium and potassium excretion.

METHODS

Population

All participants in ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial)¹⁶ and the TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease)¹⁷ trials who provided a baseline urinary sample were included in the current analyses. Participants were recruited from 733 centers in 40 countries (November 2001–May 2004). Both trials included patients at high risk of CV disease (aged ≥ 55 years with established CV disease or high-risk diabetes mellitus). Patients were ineligible if they had heart failure, low ejection fraction, significant valvular disease, serum creatinine greater than 3.0 mg/dL (265 $\mu\text{mol/L}$), renal artery stenosis, nephrotic range proteinuria, or blood pressure higher than 160/100 mm Hg.

ONTARGET was a randomized controlled trial comparing the effects of daily

use of ramipril 10 mg to telmisartan 80 mg or to their combination in 25 620 patients. TRANSCEND was a randomized controlled trial comparing daily use of telmisartan 80 mg to placebo in 5926 participants intolerant to angiotensin-converting enzyme (ACE) inhibitors. After randomization, patients underwent follow-up for a median of 56 months (final follow-up March 2008), and episodes of death, myocardial infarction (MI), stroke, and congestive heart failure (CHF) were recorded prospectively and adjudicated centrally. We combined the 2 cohorts because both trials recruited participants from the same sites, the same time period, using the same eligibility criteria (except that participants in TRANSCEND had a history of intolerance to ACE inhibitors), and used the same methods to capture baseline clinical data and outcome measures.

Approval was obtained from the institutional ethics committee of each center and all participants provided written informed consent.

Collection of Urine and Laboratory Analysis

A morning fasting urine sample was obtained from 28 880 participants (91.6%) before the run-in period of the trial. All samples were stored at the Hamilton Research Laboratory (central laboratory) or regional laboratory, Beijing, China. Urine samples were shipped to the laboratory in ambient packaging using STP 250 ambient specimen shipping boxes. Sodium and potassium concentration in each urine specimen were determined by indirect potentiometry using the Beckman Coulter Synchron Clinical System. Creatinine was determined for each urine specimen with a Roche Hitachi 917 analyzer using an enzymatic colorimetric assay with a sensitivity in urine of 54 $\mu\text{mol/L}$, a within-run imprecision of 0.8%, and a between-run imprecision of 2.1% at a urine concentration of 2120 $\mu\text{mol/L}$.

Estimated 24-Hour Urinary Sodium and Potassium Excretion

The Kawasaki formula was used to estimate 24-hour sodium and potassium

urinary excretion from a fasting morning urine sample.¹⁸ Previous studies have reported that this approach provides a valid estimate of sodium intake in healthy control participants¹⁸ and patients taking antihypertensive therapy,¹⁹ and has been used in previous studies.^{20–22}

Additional Assessment of Validity and Reliability of Urinary Sodium

The Kawasaki formula was developed and validated in an Asian population. We determined the correlation between estimated sodium excretion from fasting morning urine samples (using the Kawasaki formula) and actual 24-hour urine in a subgroup of participants included in the population-based PURE (Prospective Urban Rural Epidemiological) study²³ ($n=105$), Hamilton, Ontario, Canada. The Pearson correlation between formula-estimated and actual 24-hour urinary sodium and potassium levels was 0.55 ($P < .001$) and 0.43 ($P < .001$), respectively. By comparison, in the TONE (Trial of Nonpharmacologic Interventions in the Elderly) trial,²⁴ the correlations between 24-hour dietary recall and 24-hour urinary measurement were 0.30 for sodium and 0.43 for potassium. We also repeated the urinary measures ($n=97$) after 1 to 3 months and the test-retest correlation was 0.52 ($P < .001$) and 0.62 ($P < .001$) for formula-estimated 24-hour sodium and potassium excretion, and were 0.67 ($P < .001$) and 0.42 ($P < .001$) for actual 24-hour urinary sodium and potassium excretion. In the current cohort (participants in the ONTARGET and TRANSCEND trials), we repeated urinary measurements at 2-year follow-up and final visit in a subsample ($n=2625$). The correlation coefficients between baseline and 2-year measurements were 0.33 ($P < .001$) for sodium and 0.44 ($P < .001$) for potassium and between 2-year and final visit were 0.29 ($P < .001$) for sodium and 0.41 ($P < .001$) for potassium (eTable 1 available at <http://www.jama.com>). These correlations are comparable with those reported for repeated 24-hour urine collections in the Intersalt study,²⁵

TONE trial,²⁴ and Trials of Hypertension Prevention.²⁶

In the PURE study,²³ we also evaluated the association between formula-estimated sodium excretion and blood pressure in participants without a history of hypertension and not taking antihypertensive medications (n = 248). The mean blood pressure for lowest and highest quartiles of sodium excretion were 124.5/77.5 mm Hg vs 132.0/82.5

mm Hg (P = .005) for a mean sodium excretion difference of 2.9 g per day (adjusted for age and sex), which is similar to estimates of association from meta-analyses of randomized trials.³

Statistical Analysis

Baseline differences in characteristics between different sodium and potassium excretion categories were compared using χ^2 test and analysis of variance

(ANOVA). Based on initial exploration of the data for the primary outcome measure (composite of CV death, MI, stroke, and hospitalization for CHF), which revealed a nonlinear association between sodium excretion and CV outcomes, we initially analyzed sodium and potassium excretion as continuous variables, fitting a restricted cubic spline function with 4 knots (located at the 5th, 35th, 65th, and 95th percentiles).²⁷ Group me-

Table 1. Baseline Patient Characteristics by 24-Hour Sodium Excretion Range^a

Variable	Overall (N = 28 880)	Sodium Excretion, g/d ^b					P Value
		<2 (n = 818)	2-3.99 (n = 8353)	4-5.99 (n = 14 156)	6-8 (n = 4706)	>8 (n = 847)	
Sodium excretion, mean (SD), g/d	4.77 (1.61)	1.55 (0.35)	3.24 (0.53)	4.93 (0.56)	6.71 (0.53)	9.40 (1.81)	<.001
Potassium excretion, mean (SD), g/d	2.19 (0.57)	1.81 (0.43)	2.03 (0.48)	2.19 (0.51)	2.40 (0.55)	2.93 (1.16)	<.001
Age, mean (SD), y	66.52 (7.22)	67.61 (7.62)	67.04 (7.42)	66.46 (7.15)	65.79 (6.95)	65.37 (6.75)	<.001
Women	8504 (29.4)	438 (53.5)	3172 (38.0)	3764 (26.6)	952 (20.2)	178 (21.0)	<.001
White/European ^c	20 628 (71.4)	521 (63.7)	5851 (70.0)	10 249 (72.4)	3387 (72.0)	620 (73.2)	<.001
Previous medical history							
Myocardial infarction	13 967 (48.4)	381 (46.6)	4024 (48.2)	6942 (49.0)	2235 (47.5)	385 (45.5)	.08
Stroke/TIA	6118 (21.2)	190 (23.2)	1916 (22.9)	2860 (20.2)	960 (20.4)	192 (22.7)	<.001
Hypertension	20 200 (69.9)	640 (78.2)	5761 (69.0)	9616 (67.9)	3488 (74.1)	695 (82.1)	<.001
Diabetes mellitus	10 717 (37.1)	320 (39.1)	2691 (32.2)	5128 (36.2)	2141 (45.5)	437 (51.6)	<.001
Lifestyle risk factors							
Vegetables, mean (SD), servings/d	1.94 (1.83)	1.90 (2.14)	1.89 (1.90)	1.96 (1.79)	1.96 (1.77)	1.88 (1.52)	.03
Fruit, mean (SD), servings/d	1.79 (1.83)	1.94 (1.74)	1.85 (1.92)	1.78 (1.82)	1.70 (1.72)	1.69 (1.78)	<.001
Current smoker	3502 (12.1)	89 (10.9)	1134 (13.6)	1672 (11.8)	524 (11.1)	83 (9.8)	<.001
Mainly sedentary lifestyle	6486 (22.5)	248 (30.3)	1950 (23.3)	3030 (21.4)	1055 (22.4)	203 (24.0)	<.001
BMI, mean (SD) ^d	28.10 (4.55)	27.32 (4.63)	27.48 (4.51)	28.05 (4.38)	29.13 (4.70)	30.17 (5.09)	<.001
Atrial fibrillation							
Baseline	959 (3.3)	42 (5.1)	297 (3.6)	413 (2.9)	175 (3.7)	32 (3.8)	<.001
Follow-up	2643 (9.2)	97 (11.9)	766 (9.2)	1242 (8.8)	447 (9.5)	91 (10.7)	.01
SBP, mean (SD), mm Hg							
Baseline	141.72 (17.29)	138.61 (17.63)	140.81 (17.32)	141.96 (17.39)	142.95 (16.80)	142.93 (17.01)	<.001
Change at follow-up	-5.54 (21.77)	-1.84 (22.61)	-5.22 (22.04)	-5.91 (21.73)	-5.81 (21.10)	-4.64 (22.33)	<.001
Heart rate, beats/min, mean (SD)							
Baseline	67.98 (12.16)	69.68 (12.22)	68.12 (12.32)	67.49 (12.15)	68.61 (11.85)	69.54 (11.88)	<.001
Follow-up	69.11 (8.88)	69.80 (8.97)	69.02 (8.89)	68.83 (8.89)	69.80 (8.85)	70.26 (8.49)	<.001
Laboratory values, mean (SD)							
HDL, mmol/L	1.26 (0.41)	1.28 (0.41)	1.28 (0.41)	1.26 (0.41)	1.25 (0.41)	1.23 (0.36)	<.001
LDL, mmol/L	2.94 (0.98)	2.94 (1.06)	2.94 (1.00)	2.93 (0.97)	2.95 (0.98)	2.99 (0.98)	.24
Creatinine, μ mol/L	93.92 (24.41)	95.55 (27.47)	94.15 (25.18)	93.82 (23.80)	93.54 (24.05)	93.75 (25.72)	.22
Medications							
β -Blocker	16 529 (57.2)	476 (58.2)	4857 (58.1)	8074 (57.0)	2647 (56.2)	475 (56.1)	.22
Diuretic	8299 (28.7)	335 (41.0)	2568 (30.7)	3663 (25.9)	1366 (29.0)	367 (43.3)	<.001
Calcium antagonist	9986 (34.6)	363 (44.4)	2700 (32.3)	4572 (32.3)	1921 (40.8)	430 (50.8)	<.001
Ramipril	7851 (27.2)	210 (25.7)	2278 (27.3)	3859 (27.3)	1291 (27.4)	213 (25.1)	.57
Telmisartan	10 518 (36.4)	296 (36.2)	3082 (36.9)	5090 (36.0)	1750 (37.2)	300 (35.4)	.45
Ramipril plus telmisartan	7792 (27.0)	206 (25.2)	2215 (26.5)	3889 (27.5)	1247 (26.5)	235 (27.7)	.31

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TIA, transient ischemic attack.

SI conversion factors: To convert HDL and LDL to mg/dL, divide by 0.0259; to convert creatinine to mg/dL, divide by 88.4.

^aCategorical variables cells are reported as No. (%) and continuous variables are reported as mean (SD).

^bEquivalence of sodium excretion g per day/salt intake g per day: <2 \approx <5; 2-3.99 \approx 5-9.9; 4-5.99 \approx 10-14.9; 6-8 \approx 15-20; >8 \approx >20.

^cRace/ethnicity was self-reported.

^dBMI is calculated as the weight in kilograms divided by height in meters squared. Sedentary lifestyle was based on a questionnaire that asked participants, "How often do you engage in physical activity?" with the following response options: "mainly sedentary (reference standard), once per week, 2-4 times per week, 5-6 times per week, and everyday."

dian was chosen to be the reference group for all spline plots (4.66 g/d for sodium and 2.11 g/d for potassium). Based on restricted cubic spline analysis for sodium excretion and the composite CV outcome, we selected 4 to 5.99 g per day as the reference category because this was the range associated with the lowest risk of all CV events (multivariable cubic spline plots revealed significance thresholds at 3.87 g/d and 6.50 g/d). For potassium excretion, we used less than 1.5 g per day as the reference group.

We estimated the risk of CV events associated with estimated 24-hour urinary sodium and potassium excretion using Cox proportional hazards models for each of the following outcomes: composite outcome (CV mortality, MI, stroke, and hospitalization for CHF), CV

mortality, non-CV mortality, MI, stroke, and hospitalization for CHF. All models were adjusted for variables known to increase or reduce the risk of CV events: age, sex, race/ethnicity, prior stroke or MI, creatinine, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), hypertension, diabetes mellitus, atrial fibrillation, smoking, low-density lipoprotein (LDL), high-density lipoprotein (HDL), treatment allocation and treatment with statins, β -blockers, diuretics, calcium antagonist, and anti-thrombotic therapy, fruit and vegetable consumption, level of exercise, urinary sodium and potassium excretion, baseline blood pressure, and change in systolic blood pressure from baseline to last follow-up.

Since some of these variables may be in the causal pathway for an association between sodium or potassium intake and CV events, we also generated a model that did not include baseline blood pressure, change in blood pressure on follow-up, fruit and vegetable intake, and urinary potassium (for models of sodium excretion). We performed subgroup analyses for key characteristics that might modify the association between sodium, potassium, and CV events (age, race/ethnicity, sex, BMI, previous stroke, MI, hypertension, sodium or potassium excretion, and diuretic therapy), and statistical interaction was tested using the Wald test. To explore the potential for reverse causation, we performed analyses that excluded all events during the

Table 2. Association Between Estimated 24-Hour Urinary Sodium Excretion and CV Events and Mortality^a

	HR (95% CI) by Sodium Excretion, g/d						
	<2 (n = 818)	2-2.99 (n = 2654)	3-3.99 (n = 5699)	4-5.99 (n = 14 156)	6-6.99 (n = 3380)	7-8 (n = 1326)	>8 (n = 847)
Composite outcome, No. (%) ^b	165 (20.2)	482 (18.2)	918 (16.1)	2148 (15.2)	568 (16.8)	244 (18.4)	204 (24.1)
Univariate	1.37 (1.17-1.61)	1.22 (1.11-1.35)	1.07 (0.99-1.15)	1 [Reference]	1.13 (1.03-1.24)	1.23 (1.08-1.41)	1.69 (1.47-1.95)
Multivariable	1.21 (1.03-1.43)	1.16 (1.04-1.28)	1.06 (0.98-1.14)	1 [Reference]	1.09 (0.99-1.20)	1.15 (1.00-1.32)	1.49 (1.28-1.75)
Without BP, fruit and vegetables, and potassium excretion	1.21 (1.03-1.43)	1.15 (1.04-1.28)	1.06 (0.98-1.14)	1 [Reference]	1.09 (0.99-1.20)	1.14 (0.99-1.31)	1.48 (1.27-1.71)
Without events during year 1	1.28 (1.06-1.54)	1.14 (1.01-1.29)	1.07 (0.97-1.17)	1 [Reference]	1.09 (0.98-1.22)	1.11 (0.94-1.30)	1.49 (1.25-1.79)
Excluding all cancer	1.23 (1.03-1.47)	1.16 (1.04-1.30)	1.06 (0.97-1.16)	1 [Reference]	1.11 (1.00-1.23)	1.08 (0.93-1.26)	1.50 (1.27-1.77)
All death, No. (%)	123 (15.0)	359 (13.5)	683 (12.0)	1537 (10.9)	404 (12.0)	183 (13.8)	141 (16.6)
Univariate	1.42 (1.18-1.71)	1.27 (1.13-1.42)	1.11 (1.01-1.21)	1 [Reference]	1.12 (1.00-1.24)	1.29 (1.11-1.51)	1.60 (1.34-1.90)
Multivariable	1.19 (0.99-1.45)	1.11 (0.99-1.26)	1.06 (0.96-1.16)	1 [Reference]	1.14 (1.02-1.28)	1.29 (1.10-1.52)	1.56 (1.30-1.89)
CV death, No. (%)	87 (10.6)	227 (8.6)	403 (7.1)	886 (6.3)	230 (6.8)	129 (9.7)	95 (11.2)
Univariate	1.75 (1.40-2.18)	1.39 (1.20-1.61)	1.13 (1.01-1.27)	1 [Reference]	1.10 (0.95-1.27)	1.58 (1.31-1.90)	1.87 (1.51-2.30)
Multivariable	1.37 (1.09-1.73)	1.19 (1.02-1.39)	1.09 (0.96-1.23)	1 [Reference]	1.11 (0.96-1.29)	1.53 (1.26-1.86)	1.66 (1.31-2.10)
Non-CV death, No. (%)	36 (4.4)	132 (5.0)	280 (4.9)	651 (4.6)	174 (5.1)	54 (4.1)	46 (5.4)
Univariate	0.98 (0.70-1.38)	1.10 (0.91-1.33)	1.07 (0.93-1.23)	1 [Reference]	1.14 (0.96-1.34)	0.90 (0.68-1.19)	1.23 (0.91-1.66)
Multivariable	0.92 (0.65-1.29)	1.00 (0.83-1.21)	1.02 (0.88-1.18)	1 [Reference]	1.18 (0.99-1.40)	0.95 (0.71-1.27)	1.42 (1.04-1.94)
MI, No. (%)	42 (5.1)	123 (4.6)	277 (4.9)	655 (4.6)	189 (5.6)	68 (5.1)	58 (6.8)
Univariate	1.14 (0.83-1.55)	1.02 (0.84-1.23)	1.05 (0.92-1.21)	1 [Reference]	1.23 (1.04-1.44)	1.12 (0.87-1.44)	1.55 (1.18-2.03)
Multivariable	1.10 (0.80-1.53)	1.04 (0.85-1.27)	1.11 (0.96-1.28)	1 [Reference]	1.21 (1.03-1.43)	1.11 (0.85-1.44)	1.48 (1.11-1.98)
CHF, No. (%)	52 (6.4)	137 (5.2)	242 (4.2)	532 (3.8)	137 (4.1)	58 (4.4)	55 (6.5)
Univariate	1.75 (1.32-2.33)	1.40 (1.16-1.69)	1.13 (0.97-1.32)	1 [Reference]	1.09 (0.90-1.32)	1.18 (0.90-1.55)	1.81 (1.37-2.39)
Multivariable	1.29 (0.95-1.74)	1.23 (1.01-1.49)	1.07 (0.91-1.25)	1 [Reference]	1.04 (0.86-1.27)	1.06 (0.79-1.42)	1.51 (1.12-2.05)
Stroke, No. (%)	40 (4.9)	130 (4.9)	250 (4.4)	601 (4.2)	141 (4.2)	64 (4.8)	56 (6.6)
Univariate	1.18 (0.86-1.62)	1.17 (0.97-1.42)	1.04 (0.90-1.20)	1 [Reference]	1.00 (0.83-1.20)	1.15 (0.89-1.49)	1.62 (1.23-2.13)
Multivariable	1.06 (0.76-1.46)	1.05 (0.86-1.28)	0.97 (0.83-1.13)	1 [Reference]	0.95 (0.79-1.15)	1.06 (0.81-1.40)	1.48 (1.09-2.01)

Abbreviations: BP, blood pressure; CHF, congestive heart failure; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

^aUnless stated, model adjusted for age, sex, race/ethnicity (white vs nonwhite), prior history of stroke or myocardial infarction, creatinine, body mass index, comorbid vascular risk factors (hypertension, diabetes mellitus, atrial fibrillation, smoking, low-density lipoprotein, and high-density lipoprotein), treatment allocation (ramipril, telmisartan, or both, and treatment with statins, β -blockers, diuretic therapy, calcium antagonist, and antithrombotic therapy), fruit and vegetable consumption, level of exercise, baseline blood pressure and change in systolic blood pressure from baseline to last follow-up, and urinary potassium.

^bComposite outcome includes CV mortality, MI, stroke, and hospitalization for CHF.

first year of follow-up, and analyses that excluded patients with previous history of cancer or cancer during follow-up. To explore the effect of regression dilution bias, we conducted a secondary analysis using “usual” excretion of sodium/potassium. To calculate usual excretion, we used the method described by Lewington et al²⁸ (using regression dilution ratio that was calculated from baseline measurement and remeasurement at 2 years in 2625 participants). The assumptions of proportional hazard of sodium/potassium were assessed by fitting a model of primary outcome with interaction terms between the survival time and sodium ($P=.95$) and potassium ($P=.53$) groups.

A priori, a 2-tailed P value of less than .05 was considered statistically significant. All analyses were conducted using SAS version 8.2 for Unix.

RESULTS

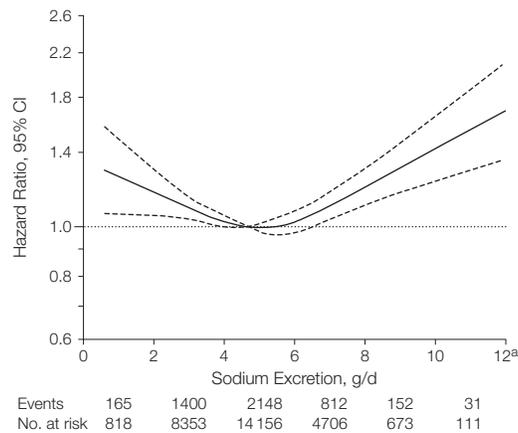
In total, 31 546 were enrolled, of whom 28 880 participants (91.6%) provided a baseline morning fasting urine sample. Loss to follow-up was 0.2%, and median follow-up was 56 months (25th-75th percentiles, 53-60 months). The overall mean (SD) estimated 24-hour sodium excretion was 4.77 g (1.61) (TABLE 1) and potassium excretion was 2.19 g (0.57) (eTable 2).

24-Hour Sodium Excretion and Risk of Death and CV Events

TABLE 2 shows 24-hour sodium excretion and risk of death and CV events. Restricted multivariable cubic spline plots for all outcomes are presented in FIGURE 1 and FIGURE 2A-D.

Composite Outcome. The composite outcome occurred in 4729 (16.4%) participants. Compared with baseline sodium excretion of 4 to 5.99 g per day ($n=14\ 156$ [15.2% with the composite outcome]), higher baseline sodium excretion (18.4% [HR 1.15; 95% CI, 1.00-1.32] for 7-8 g/d and 24.1% [HR, 1.49; 95% CI, 1.28-1.75] for >8 g/d) and lower sodium excretion (18.2% [HR, 1.16; 95% CI, 1.04-1.28] for 2-2.99 g/d and 20.2% [HR, 1.21; 95% CI, 1.03-1.43] for <2g/d) were associated with an increased risk of

Figure 1. Estimated 24-Hour Urinary Excretion of Sodium and Composite of Cardiovascular Death, Stroke, Myocardial Infarction, and Hospitalization for Congestive Heart Failure



Spline plot for adjusted Cox models. Median intake is reference standard. Salt approximates $2.5 \times$ sodium g per day. Model was adjusted for age, sex, race/ethnicity (white vs nonwhite); prior history of stroke or myocardial infarction; creatinine, body mass index; comorbid vascular risk factors (hypertension, diabetes mellitus, atrial fibrillation, smoking, low- and high-density lipoprotein); treatment allocation (ramipril, telmisartan, neither, or both); treatment with statins, β -blockers, diuretic therapy, calcium antagonist, and antithrombotic therapy; fruit and vegetable consumption, level of exercise; baseline blood pressure and change in systolic blood pressure from baseline to last follow-up; and urinary potassium. Dashed lines indicate 95% CIs. Events and numbers at risk are shown between values on x-axis because they indicate the numeric range between these values.

^aSpline curve truncated at 12 g per day (63 participants had sodium excretion >12 g/d, event rate 21/63).

the composite of CV death, MI, stroke, and hospitalization for CHF on multivariable analysis.

Mortality. Overall, 3430 (11.9%) participants died during follow-up, of which 2057 deaths (60%) were from a CV cause. Compared with baseline sodium excretion of 4 to 5.99 g per day (6.3% with CV death), higher baseline sodium excretion (9.7%; [HR, 1.53; 95% CI, 1.26-1.86] for 7-8 g/d, 11.2%; [HR, 1.66; 95% CI, 1.31-2.10] for >8 g/d) and lower sodium excretion (8.6%; [HR, 1.19; 95% CI, 1.02-1.39] for 2-2.99 g/d, 10.6%; [HR, 1.37; 95% CI, 1.09-1.73] for <2 g/d) were associated with an increased risk of CV death.

MI, Stroke, and Hospitalization for CHF. MI occurred in 1412 (4.9%), stroke occurred in 1282 (4.4%), and hospitalization for CHF in 1213 (4.2%) participants. Compared with baseline sodium excretion of 4 to 5.99 g per day (4.6% patients with MI, 4.2% with stroke, and 3.8% hospitalized for CHF), higher baseline sodium excretion was associated with an increased risk of MI (5.6%; [HR, 1.21; 95% CI, 1.03-1.43] for 6-6.99 g/d and 6.8%; [HR, 1.48; 95%

CI, 1.11-1.98] for >8 g/d), stroke (6.6%; [HR, 1.48; 95% CI, 1.09-2.01] for >8 g/d) and hospitalization for CHF (6.5%; [HR, 1.51; 95% CI, 1.12-2.05] for >8 g/d), while lower sodium excretion was associated with an increased risk of hospitalization for CHF (5.2%; [HR, 1.23; 95% CI, 1.01-1.49] for 2-2.99 g/d).

Sensitivity/Subgroup Analyses. The exclusion of blood pressure (baseline and follow-up), fruit and vegetable intake, and potassium excretion from the Cox model did not materially influence our findings (Table 2). Our results were not materially altered by excluding events that occurred in the first 12 months or by excluding participants with previous or incident cancer (Table 2). In subgroup analyses, none of the selected covariates was a significant effect modifier of the association between sodium excretion and CV events (eTable 3). Correcting for regression dilution bias using usual excretion of sodium and potassium, we observed a stronger magnitude of association for the composite outcome due to compression of the distribution of sodium excretion (eFigure).

24-Hour Potassium Excretion and Risk of Death and CV Events

Mortality, MI, and CHF. There was no significant association between potassium excretion and CV mortality, MI, and hospitalization for CHF (eTable 4).

Stroke. Compared with an excretion of less than 1.5 g per day (n=2194 [6.2% with stroke]), higher potassium excretion was associated with a reduced risk of stroke (4.7% [HR, 0.77; 95% CI, 0.63-0.94] for 1.5-1.99 g/d;

4.3% [HR, 0.73; 95% CI, 0.59-0.90] for 2-2.49 g/d; 3.9% [HR, 0.71; 95% CI, 0.56-0.91] for 2.5-3 g/d; and 3.5% [HR, 0.68; 95% CI, 0.49-0.92] for >3 g/d; eTable 4) on multivariable analysis.

FIGURE 3 presents restricted multivariable cubic spline plot.

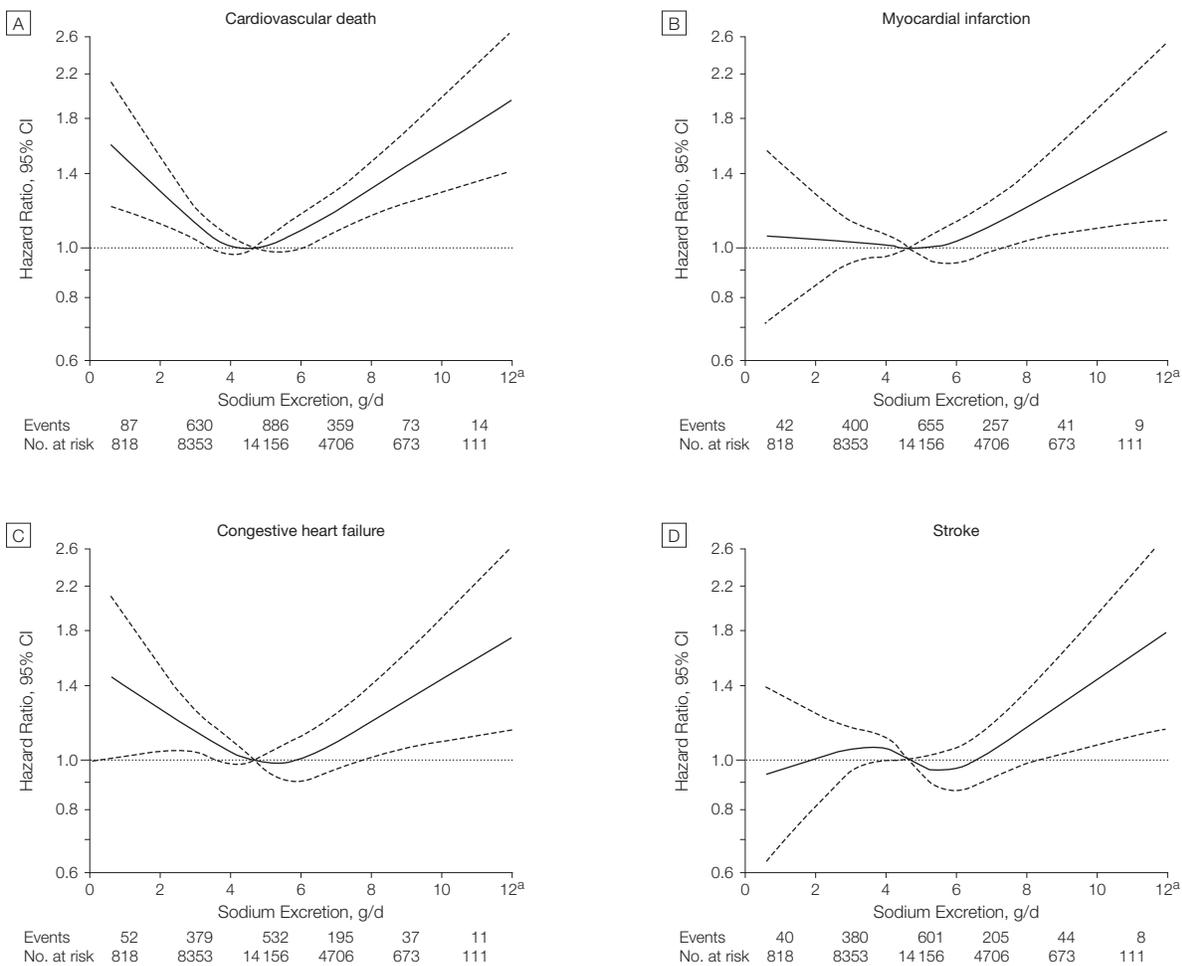
Interaction Between Sodium and Potassium Excretion. There was no significant interaction between sodium and potassium excretion for the composite outcome measure (P=.45), CV

death (P=.46), hospitalization for CHF (P=.62), and stroke (P=.48) (TABLE 3), non-CV death (P=.30), or MI (P=.84).

COMMENT

We found a J-shaped association between estimated sodium excretion and CV events. Compared with baseline sodium excretion of 4 to 5.99 g per day, sodium excretion of more than 7 g per day was associated with an increased risk of all CV events while a sodium ex-

Figure 2. Estimated 24-Hour Urinary Excretion of Sodium and Cardiovascular Death, Myocardial Infarction, Hospitalization for Congestive Heart Failure, and Stroke



Spline plot for adjusted Cox models. Median intake is reference standard. Salt approximates 2.5 × sodium g per day. Model was adjusted for age, sex, race/ethnicity (white vs nonwhite); prior history of stroke or myocardial infarction; creatinine, body mass index; comorbid vascular risk factors (hypertension, diabetes mellitus, atrial fibrillation, smoking, low- and high-density lipoprotein); treatment allocation (ramipril, telmisartan, neither, or both); treatment with statins, β-blockers, diuretic therapy, calcium antagonist, and antithrombotic therapy; fruit and vegetable consumption, level of exercise; baseline blood pressure and change in systolic blood pressure from baseline to last follow-up; and urinary potassium. Dashed lines indicate 95% CIs. Events and numbers at risk are shown between values on x-axis because they indicate the numeric range between these values.

^aSpline curve truncated at 12 g per day (63 participants had sodium excretion >12 g/d; event rate, 8/63 for cardiovascular death and for myocardial infarction, 7/63 for congestive heart failure, and 4/63 for stroke).

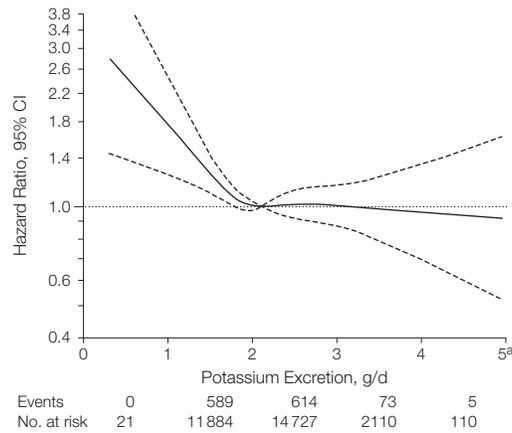
cretion of less than 3 g per day was associated with increased risk of CV mortality and hospitalization for CHF. We found an association between higher estimated potassium excretion and reduction in stroke risk, but did not find evidence of statistical interaction between sodium and potassium excretion for any outcome.

A recent meta-analysis²⁹ of 13 prospective studies reported that a 5-g increase in salt (2 g of sodium) was associated with a 23% increase in stroke and a 14% increase in CV disease. We extend these findings by providing evidence (based on 29 000 individuals and >6000 events) of an association within each individual CV outcome in high-risk patients. Our findings emphasize the burden of CV disease associated with excess sodium intake and the importance of population-based programs to reduce sodium intake in populations consuming high-sodium diets.³⁰

However, we did not observe a significant association until sodium excretion exceeded 6.5 g per day (Figure 1), a threshold that is higher than that recommended by the WHO and many national guidelines^{31,32} (recommended thresholds generally range from <2.3 to <1.5 g/d) but closer to the threshold suggested by Alderman and Cohen's critical interpretation of the totality of evidence (>4-5 g/d).^{1,33}

Against this, a number of trials (eg, DASH [Dietary Approaches to Stop Hypertension] and TOHP [Trials of Hypertension Prevention Collaborative Research Group]^{34,35}) have found that by reducing sodium excretion and targeting levels consistent with current guidelines, blood pressure was reduced in those with and without hypertension.^{3,36} The TOHP trials, which included younger patients with high-normal blood pressure, did not report a difference in CV events on initial follow-up, but during an extended observational follow-up of 10 to 15 years reported a nonsignificant benefit, which became statistically significant after multivariable adjustment.³⁷ Therefore, these studies are suggestive but not conclusive of a benefit from sodium reduc-

Figure 3. Estimated 24-Hour Urinary Excretion of Potassium and Stroke



Spline plot for adjusted Cox models. Median excretion is the reference standard. Model adjusted for age, sex, race/ethnicity (white vs nonwhite); prior history of stroke or myocardial infarction; creatinine, body mass index; comorbid vascular risk factors (hypertension, diabetes mellitus, atrial fibrillation, smoking, low- and high-density lipoprotein); treatment allocation (ramipril, telmisartan, neither, or both); treatment with statins, β -blockers, diuretic therapy, calcium antagonist, and antithrombotic therapy; fruit and vegetable consumption, level of exercise; baseline blood pressure and change in systolic blood pressure from baseline to last follow-up, and urinary sodium. Dashed lines indicate 95% CIs. Events and numbers at risk are shown between values on x-axis because they indicate the numeric range between these values.

^aSpline curve truncated at 5 g per day (29 participants had potassium excretion >5 g/d, event rate 1/29).

tion to low-intake targets in a primary prevention population. However, a recent Cochrane review³⁸ of randomized controlled trials evaluating reduced sodium intake did not detect a significant reduction in CV mortality or morbidity, but did report an increased risk of all-cause mortality in those with a previous history of CHF who were randomized to sodium restriction (based on the results of a single trial³⁹). There is some observational evidence that dietary-related reductions in blood pressure may not necessarily translate into CV disease prevention,⁴⁰ particularly if sodium intake is linked with other adverse dietary factors. Another meta-analysis, which included primary prevention trials only, reported a marginally significant reduction in CV events in the group randomized to reduced sodium intake.⁴¹ In contrast with populations included in most previous randomized controlled trials and most epidemiological studies, our study population was at higher CV risk because most had a history of a CV event and, as such, may be more susceptible to extremes of sodium intake.^{39,42,43}

For CV mortality, we report a J-shaped association with estimated urinary sodium excretion. A recent study⁴³ reported a J-shaped association between sodium excretion and all-cause mortality in patients with type 1 diabetes mellitus, but did not report on CV mortality or CV events. Previous individual prospective cohort studies have either reported a positive association, no association, or an inverse relationship between sodium intake and CV mortality.⁴⁻¹³ Discrepant findings of previous studies are likely due to differences in ranges of sodium intake, study populations, methods of measurement, and failure to explore a nonlinear association. For example, the NHANES-II study,¹² the first to report an association between low sodium intake and CV mortality, had a mean sodium intake of 2.7 g per day while the studies reporting the strongest association between high sodium intake and CV mortality had mean intakes of about 4 g per day.⁴⁻⁶ The recent FLEMENGHO/EPOGH (Flemish Study on Genes, Environment, and Health Outcomes/European Project on Genes in Hypertension) cohort study¹³ also re-

ported an increased risk in CV mortality associated with low sodium excretion (group mean, 2.3 g/d) but, unlike our study, it did not report an increased risk with high sodium excretion, likely due to smaller sample size and fewer CV events in a population at lower CV risk. Clearly, large randomized controlled trials evaluating the effect of reduced sodium intake in primary and secondary prevention populations, within a multifactorial dietary intervention, on CV outcomes in those with moderate sodium intake are needed urgently.¹ Pending the results of such trials, a more cautious approach to policy on sodium intake may be appropriate, one that targets sodium reduction in populations consuming high sodium levels and reflects the uncertainty in those with moderate sodium diets, which includes the majority of the population.

A number of mechanisms are proposed to explain an increased CV mortality associated with low sodium intake, which include hypotension, activation of the renin-angiotensin and sympathetic nervous system, metabolic effect on lipoproteins and insulin, and negative balance of magne-

sium calcium.⁴⁴ Of note, we observed that the increased mortality in the low excretion groups was confined to CV causes of death with no effect on non-CV death (Table 2). Our finding of an association between low sodium intake and hospitalization for CHF may suggest that activation of the renin-angiotensin system may play a role,⁴⁴ which is consistent with the results of a small randomized controlled trial comparing moderate to low sodium intake in patients with established CHF.³⁹ This trial reported an increased risk of rehospitalization in the low-sodium intake group and association with increased aldosterone and plasma renin activity compared with the moderate intake group.³⁹

We observed an inverse relationship between estimated 24-hour urinary potassium and stroke risk, also reported in previous studies and a recent meta-analysis.¹⁴ Proposed mechanisms to explain the association include a blood pressure lowering effect,⁴⁵ a modifying effect on sodium intake, or that healthy dietary patterns are high in potassium.⁴⁶ In our study, we did not observe a higher baseline blood pres-

sure in the group with lower compared with higher potassium excretion. Although we did not observe significant interaction between potassium and sodium excretion, the lowest CV event rates occurred in the group with moderate sodium excretion and high potassium excretion (Table 3). Participants with higher potassium excretion reported higher daily intake of fruit, but the association between potassium excretion and stroke remained significant after adjusting for fruit intake (eTable 2). At present, it is not clear why potassium excretion has a stronger association with stroke risk compared with other CV outcomes.

Our method of estimating sodium and potassium excretion (and indirectly, intake) may be considered both a strength and limitation. A simple, objective measure of population-level sodium and potassium intake holds enormous importance as it allows convenient monitoring in large-scale studies. It is accepted that a single urine measurement of sodium intake lacks precision for individuals, but provides a more accurate measure of sodium intake at a population level.⁴⁷ Although

Table 3. Association Between Sodium Excretion and CV Events by Potassium Excretion Categories^a

	Sodium \leq 3.99 g/d (n = 9171)		Sodium 4-5.99 g/d (n = 14 155)		Sodium \geq 6 g/d (n = 5553)	
	No. of Patients/Events (%)	HR (95% CI)	No. of Patients/Events (%)	HR (95% CI)	No. of Patients/Events (%)	HR (95% CI)
Composite outcome						
All	1565/9171 (17.1)	1.10 (1.03-1.18)	2148/14155 (15.2)	1 [Reference]	1016/5553 (18.3)	1.16 (1.07-1.25)
Potassium <1.5 g/d (n = 2194)	222/1240 (17.9)	1.10 (0.88-1.37)	137/862 (15.9)	1 [Reference]	16/92 (17.4)	1.15 (0.66-2.02)
Potassium 1.5-3 g/d (n = 24 436)	1303/7634 (17.1)	1.10 (1.02-1.19)	1888/12306 (15.3)	1 [Reference]	808/4496 (18.0)	1.12 (1.03-1.22)
Potassium >3 g/d (n = 2249)	40/297 (13.5)	1.00 (0.69-1.46)	123/987 (12.5)	1 [Reference]	192/965 (19.9)	1.38 (1.08-1.77)
CV death						
All	717/9171 (7.8)	1.15 (1.03-1.27)	886/14155 (6.3)	1 [Reference]	454/5553 (8.2)	1.29 (1.15-1.46)
Potassium <1.5 g/d (n = 2194)	116/1240 (9.4)	1.47 (1.04-2.09)	48/862 (5.6)	1 [Reference]	9/92 (9.8)	1.92 (0.89-4.16)
Potassium 1.5-3 g/d (n = 24 436)	585/7634 (7.7)	1.12 (1.00-1.25)	792/12306 (6.4)	1 [Reference]	362/4496 (8.1)	1.24 (1.09-1.41)
Potassium >3 g/d (n = 2249)	16/297 (5.4)	1.16 (0.63-2.11)	46/987 (4.7)	1 [Reference]	83/965 (8.6)	1.46 (0.99-2.18)
Stroke						
All	420/9171 (4.6)	1.02 (0.90-1.16)	601/14155 (4.3)	1 [Reference]	261/5553 (4.7)	1.02 (0.87-1.19)
Potassium <1.5 g/d (n = 2194)	76/1240 (6.1)	0.99 (0.69-1.42)	53/862 (6.2)	1 [Reference]	6/92 (6.5)	0.91 (0.33-2.56)
Potassium 1.5-3 g/d (n = 24 436)	335/7634 (4.4)	0.99 (0.86-1.14)	525/12306 (4.3)	1 [Reference]	208/4496 (4.6)	0.99 (0.84-1.17)
Potassium >3 g/d (n = 2249)	9/297 (3.0)	1.25 (0.57-2.76)	23/987 (2.3)	1 [Reference]	47/965 (4.9)	1.66 (0.97-2.83)

Abbreviations: CV, cardiovascular; HR, hazard ratio.

^aModels were adjusted for age, sex, ethnicity (white vs nonwhite), prior history of stroke or myocardial infarction, creatinine, Body mass index (calculated as weight in kilograms divided by height in meters squared), comorbid vascular risk factors (hypertension, diabetes mellitus, atrial fibrillation, smoking, low-density lipoprotein, and high-density lipoprotein), treatment allocation (ramipril, telmisartan or both, and treatment with statins, β -blockers, diuretic therapy, calcium antagonist, and antithrombotic therapy), fruit and vegetable consumption, level of exercise, baseline blood pressure, and change in systolic blood pressure from baseline to last follow-up. *P* value for interaction was .45 for the composite outcome, .46 for CV death, and .48 for stroke.

we did not use the criterion standard for estimating sodium intake (24-hour urine), our derived estimates appear generally consistent with other studies that used 24-hour urinary measures.^{48,49} The correlation coefficients between baseline and 2-year follow-up measurements in our study were moderate but are similar to those reported for repeated 24-hour urinary collections in other studies.²⁴⁻²⁶ Inter-individual variation in day-to-day intake and excretion of sodium and intracellular and intercellular fluid retention and excretion through the skin are sources of confounding that compromise reproducibility for all methods of estimating sodium intake. A further limitation is that the Kawasaki formula was initially developed and validated in Asians free of CV disease^{18,19} while our cohort included patients at high CV risk, and the majority were non-Asian. We report a correlation coefficient between Kawasaki formula-derived estimates and 24-hour urinary estimates for sodium of 0.55 in a non-Asian population, which is stronger than the correlation reported between 24-hour urine and 24-hour dietary recall methods in the TONE trial (and 24-hour dietary recall has been used in a number of previous large studies for estimating sodium intake^{7,11,12}). Although we would expect this potential source of measurement bias to influence absolute estimates of sodium intake, it is less likely to alter the shape of association reported on cubic spline plots. Further work is required to determine the optimal approach to estimating 24-hour urinary excretion from fasting morning urine samples in different populations, and randomized controlled trials are required to determine the optimal range of sodium intake in both primary and secondary prevention populations.

Our study has a number of additional limitations, and findings should be interpreted with these in mind. First, our cohort includes participants with established CV disease recruited into a randomized controlled trial. Patients who agree to participate in a clinical trial

may have different lifestyle behaviors than those who decline participation (eg, dietary intake of sodium in our study's population may be lower than in patients in routine clinical practice). In addition, our population is at higher risk of CV events than a primary prevention cohort and may be more vulnerable to the extremes of sodium intake. As such, our results may not apply to a lower-risk population. Second, urinary excretion is influenced by a number of factors, particularly medications such as diuretics, ACE inhibitors, and angiotensin II receptor blockers. Subgroup analyses by diuretic use did not influence findings and since baseline urine collection occurred before trial run-in, patients would not have received trial medications at the time of baseline urinary collection. Third, urinary electrolytes were measured at a single time point and may not accurately reflect sodium and potassium excretion during the course of the trial. To explore the effects of regression dilution bias, we also reported estimates for usual excretion and found stronger magnitudes of association. However, our adjustment was based on approximately 10% of the population and we suspect that our analysis may have overadjusted. Therefore, these findings are presented as a secondary analysis (eFigure). In our study, participants were not receiving study medication at the time of baseline collection, which may also have influenced test-retest correlations.

Strengths include the very large number of patients and outcomes (centrally adjudicated), the international representation of the cohort, high completeness of data, use of a central laboratory for urinary electrolyte measurement, and the availability of detailed covariates to adjust for a broad range of potential confounders. To our knowledge, the current study represents the largest cohort and most diverse group of individuals with CV disease with urinary-based estimates of sodium and potassium intake.

In conclusion, our study reports a J-shaped association between esti-

mated urinary sodium excretion and CV events in those at increased CV risk. Compared with moderate sodium excretion, we found an association between high sodium excretion and CV events and low sodium excretion and CV death and hospitalization for CHF, which emphasizes the urgent need to establish a safe range for sodium intake in randomized controlled trials. Higher urinary potassium excretion was associated with lower stroke risk and is a potential intervention that merits further evaluation for stroke prevention.

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Author Contributions: Dr O'Donnell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs O'Donnell and Yusuf contributed equally to this article (joint first authors).

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Study supervision: O'Donnell, Yusuf, Manns, Teo, Sleight, Probstfield, Schmieder.

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Online-Only Material: eTables 1, 2, 3, and 4, the eFigure, and the Author Audio Interview are available at <http://www.jama.com>.

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