Urinary sodium concentration predicts time to major adverse coronary events and all-cause mortality in men with heart failure over a 28–33-year period: a prospective cohort study

Anand Ganes1*, Jessica A. Davis2, Jyrki K. Virtanen3, Ari Voutilainen3, Tomi-Pekka Tuomainen3, John J. Atherton4, John Amerena5, Andrea Driscoll6,7, Dave L. Hare8,9, Gary Wittert10, Anu Ruusunen2,3,11, Wolfgang Marx2, Mohammadreza Mohebbi12 and Adrienne O’Neil2,7

Abstract

Background: Lower urinary sodium concentrations (UNa) may be a biomarker for poor prognosis in chronic heart failure (HF). However, no data exist to determine its prognostic association over the long-term. We investigated whether UNa predicted major adverse coronary events (MACE) and all-cause mortality over 28–33 years.

Methods: One hundred and eighty men with chronic HF from the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) were included. Baseline data was collected between 1984 and 1989. MACE and all-cause outcomes were obtained using hospital linkage data (1984–2017) with a follow-up of 28–33 years. Cox proportional hazards models were generated using 24-h UNa tertiles at baseline (1 ≤ 173 mmol/day; 2 = 173–229 mmol/day; 3 = 230–491 mmol/day) as a predictor of time-to-MACE outcomes, adjusted for relevant covariates.

Results: Overall, 63% and 83% of participants (n = 114 and n = 150) had a MACE event (median 10 years) and all-cause mortality event (median 19 years), respectively. On multivariable Cox Model, relative to the lowest UNa tertile, no significant difference was noted in MACE outcome for individuals in tertiles 2 and 3 with events rates of 28% (HR:0.72; 95% CI: 0.46–1.12) and 21% (HR 0.79; 95% CI: 0.5–1.25) respectively.. Relative to the lowest UNa tertile, those in tertile 2 and 3 were 39% (HR: 0.61; 95% CIs: 0.41, 0.91) and 10% (HR: 0.90; 95% CIs: 0.62, 1.33) less likely to experience all-cause mortality. The multivariable Cox model had acceptable prediction precision (Harrell’s C concordance measure 0.72).

Conclusion: UNa was a significant predictor of all-cause mortality but not MACE outcomes over 28–33 years with 173–229 mmol/day appearing to be the optimal level. UNa may represent an emerging long-term prognostic biomarker that warrants further investigation.

Keywords: Heart failure, Biomarker, Prognosis, Translational medical research
increased hospitalisations and associated length of stay [2].

There has been a growing interest in identifying biomarkers to enable prognostication of HF [3]. One such marker is urinary sodium. Due to the haemodynamic alterations in HF, reduced renal perfusion results in increased neurohormonal activation [4]. The renin-angiotensin system upregulation aims to increase fluid retention by conserving sodium and thereby reducing UNa [5]. The reduced excretion of sodium and fluid therefore exacerbates a fluid overloaded state.

Many studies have demonstrated the association of low UNa with poorer outcomes in acute HF patients including poor diuretic response during acute hospitalisation, increased risk of re-hospitalisation and an overall higher all-cause mortality [6–8]. However, there is limited evidence on the role of urinary sodium in predicting major adverse coronary events (MACE) in individuals with chronic HF over the long term. The objective of this study is to assess the long-term relationship between UNa and MACE as well as all-cause mortality outcomes in men with HF over a period of 28–33 years.

**Methods**

**Study participants data**

Data for the current study included baseline, 24 h collection of urine which spanned 1984–1989, and incident MACE outcomes which were obtained through record linkage to national hospital discharge (Finnish Institute for Health and Welfare, Data License THL/93/5.05.00/2013) and death certificate databases (Statistics Finland, Data License TK-53-1770-16) 1984–2017. This is available from the corresponding author upon request. These data provided a follow-up period of 28–33 years. The baseline HF diagnosis refers to answering ‘yes’ to at least one of the following questions: ‘My doctor has told me that I have heart failure’ or ‘I have taken drugs for heart failure during the past seven days’. Participants were men from KIHD who had a self-reported HF diagnosis at baseline and provided 24-h urine samples (n = 180 of the n = 1956 enrolled) (Fig. 1).

**Study design**

The Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) is an ongoing, prospective population-based cohort study investigating risk factors associated with CVD, atherosclerosis and related health conditions in Eastern Finnish men. A total of 2682 men who were 42, 48, 54, or 60 years old at baseline (83% of those eligible) were recruited in two cohorts between 1984 and 1989 (Fig. 1). The study design and recruitment details have been described elsewhere [9]. The KIHD protocol was approved by the Research Ethics Committee of the University of Kuopio (December 1, 1983) and all participants provided informed consent.

**Variables of interest**

**Urinary sodium**

The exposure variable was urinary sodium excretion (UNa), expressed as millimoles per day (mmol/day), which
was categorized into tertiles. $U_{Na}$ was calculated using sodium concentrations from a 24-h urine sample, collected in the 24 h prior to the study visit at baseline. This metric is the gold standard for measuring dietary sodium intake; collections accurately reflect sodium intake for 93% of the average global population [10]. In HF patients who are not taking loop diuretic medications, 24-h $U_{Na}$ significantly correlates with dietary sodium estimates from food records of two consecutive days [11].

**MACE outcomes and all-cause mortality**

The primary outcome variable was time to major adverse coronary events (MACE) which included cardiovascular disease (CVD) death (excluding stroke death), acute myocardial infarction (AMI) death, and/or hospital presentation of AMI or unstable angina, monitored over a period of 28–33 years. Classification of suspected AMI events was coded according to the International Classification of Disease (ICD-10 codes I20 and I21-I22).

The secondary outcome was all-cause mortality which was based on register linkage to the causes of death register of Statistics Finland.

**Covariates**

Potential confounders were collected through self-reported questionnaires at baseline including dichotomized CVD family history, socio-economic status (SES), highest level of education (elementary school, elementary and vocational school, junior high, junior high and vocational school, or senior high), annual income, marital status, age, dichotomized smoker at baseline, alcohol intake (g/week), total physical activity (metabolic equivalents/hour/year), New York Heart Association classification, dichotomized currently taking medications including anti-hypertensives, beta-blockers, and anti-hypercholesterolemic agents, diagnosis of diabetes (T1DM and T2DM combined into one variable as medical knowledge at baseline did not allow for distinguishing between the two) and hypertension, and a history of mental illness added into the multivariable Cox model (Additional file 2: Table S4) [12]. Inclusion of the above variables to the urinary tertiles did not improve the precision of model prediction nor altered HR estimations for tertiles of $U_{Na}$. The proportional hazard assumptions were investigated graphically by log-log(survival)) plots for $U_{Na}$. Time to first MACE (survival) curves were illustrated using Kaplan–Meier estimator of the survival function using product limit estimator. Harrell's C concordance statistic of the Cox model resulted from the backward stepwise variable selection method were compared with potential alternative models when additional predictors including CVD family history, socio-economic status (SES), dichotomized smoker at baseline, New York Heart Association classification, diagnosis of diabetes (T1DM and T2DM), dichotomized currently taking medications including anti-hypertensives, beta-blockers, and anti-hypercholesterolemic agents, and hypertension, and history of mental illness added into the multivariable Cox model (Additional file 2: Table S1) that included tertiles of $U_{Na}$ and each potential confounder one at a time to identify important confounders. Goodness of fit measures (i.e. AIC, BIC, and Harrell’s C concordance statistic) of the Cox model were compared with potential alternative models when additional predictors including CVD family history, socio-economic status (SES), dichotomized smoker at baseline, New York Heart Association classification, diagnosis of diabetes (T1DM and T2DM), dichotomized currently taking medications including anti-hypertensives, beta-blockers, and anti-hypercholesterolemic agents, and hypertension, and history of mental illness added into the multivariable Cox model. Inclusion of the above variables to the urinary tertiles did not improve the precision of model prediction nor altered HR estimations for tertiles of $U_{Na}$. The proportional hazard assumptions were investigated graphically by log-log(survival)) plots for $U_{Na}$. Time to first MACE (survival) curves were illustrated using Kaplan–Meier estimator of the survival function using product limit estimator. Harrell's C concordance statistic was reported as a measure of model prediction precision. Values of Harrell’s C near 0.5 indicate that the risk score predictions are no better than a coin flip in determining which patient will live longer, and Harrell’s C values near 1 imply perfect concordance between risk score predictions and event times [13].

Urinary sodium was initially investigated as a continuous variable with no significant associations observed, therefore an exploratory analysis with tertiles was conducted. In additional sensitivity analysis, multivariable fractional polynomial (MFP) of continuous urinary sodium excretion was added into the model to assess non-linearity of urinary sodium as a continuous exposure to explore MACE probability pattern across follow-up period at tertiles of $U_{Na}$ and MACE rate per 1000 person years per annum and 95% confidence intervals (CI) at tertiles of $U_{Na}$ were reported. In addition, a Cox proportional hazard regression model was used to estimate the age-adjusted hazard ratios (HRs) and their 95% confidence intervals (95% CIs) for tertiles of $U_{Na}$. Potential confounders were investigated in trivariable Cox models (Additional file 1: Table S1) that included tertiles of $U_{Na}$ and each potential confounder one at a time to identify important confounders. Goodness of fit measures (i.e. AIC, BIC, and Harrell’s C concordance statistic) of the Cox model were compared with potential alternative models when additional predictors including CVD family history, socio-economic status (SES), dichotomized smoker at baseline, New York Heart Association classification, diagnosis of diabetes (T1DM and T2DM), dichotomized currently taking medications including anti-hypertensives, beta-blockers, and anti-hypercholesterolemic agents, and hypertension, and history of mental illness added into the multivariable Cox model (Additional file 2: Table S4) [12]. Inclusion of the above variables to the urinary tertiles did not improve the precision of model prediction nor altered HR estimations for tertiles of $U_{Na}$. The proportional hazard assumptions were investigated graphically by log-log(survival)) plots for $U_{Na}$. Time to first MACE (survival) curves were illustrated using Kaplan–Meier estimator of the survival function using product limit estimator. Harrell's C concordance statistic was reported as a measure of model prediction precision. Values of Harrell’s C near 0.5 indicate that the risk score predictions are no better than a coin flip in determining which patient will live longer, and Harrell’s C values near 1 imply perfect concordance between risk score predictions and event times [13].

Urinary sodium was initially investigated as a continuous variable with no significant associations observed, therefore an exploratory analysis with tertiles was conducted. In additional sensitivity analysis, multivariable fractional polynomial (MFP) of continuous urinary sodium excretion was added into the model to assess non-linearity of urinary sodium as a continuous exposure.
in the multivariable Cox model (Additional file 2: Tables S1 and S2) [14]. Competing risk model of MACE versus non cardiovascular mortality as an alternative cause of failure on continuous urinary sodium excretion was performed as a sensitivity analysis.

Statistics were conducted using Stata version 17.0.

Power calculation
A post-hoc power calculation was performed based on a total sample of 180 participants and an overall expected MACE rate of 60 per 1000 person years (extracted from the data). The study had 80% power at an alpha = 0.05 significance level to detect a minimum HR decline of 0.3 (HR = 0.7 or less) when comparing tertiles of $U_{Na}$.

Results
Sample characteristics
Table 1 displays the sample baseline characteristics by exposure level (i.e. tertile). Participants were aged between 42 and 60 years (median = 54.4 years). Half of the sample were smokers at baseline, the majority did not complete junior high school, and most reported a family history of CVD. Diuretic use was greater in tertile 3 compared to tertiles 1 and 2, and hypertension more prevalent in tertile 1 compared to tertiles 2 and 3. Over half of the cohort were taking beta blocking agents, with the highest percentage found in tertile 3. Sixty six percent and 15% had self-reported hypertension and diabetes, respectively, and 14% of participants reported both hypertension and diabetes. Details of medication class and type as well as other characteristics are displayed in Table 1.

One hundred and fourteen MACE events were recorded over median 10 (IQR 3, 17) years with n = 42, 37, and 35 MACE events across tertiles 1, 2, and 3 respectively (Table 2). The rate of event per 1000 person years was 55.89, 37.85, and 40.77, across tertiles 1, 2, and 3 respectively, with the lowest MACE events observed in tertile 2. The median follow time was across tertiles 1, 2 and 3 were 10.3 years, 14.3 years, and 12.8 years respectively.

### Table 1 Key baseline characteristics of sample

| Tertile 1 (< 173 mmol/day) (n = 61) | Tertile 2 (173–229 mmol/day) (n = 59) | Tertile 3 (230–491 mmol/day) (n = 60) | All Participants (n = 180) |
|-----------------------------------|--------------------------------------|-------------------------------------|---------------------------|
| Age, years, median (IQR)          | 54.42 (54.33, 55.00)                  | 54.42 (54.33, 60.08)                | 54.42 (54.25, 54.50)      | 54.42 (54.33, 54.75)      |
| Smoker, n (%)                     | 20 (32.79)                           | 13 (22.03)                          | 15 (25.00)                | 48 (26.67)                |
| Education level, n (%)            |                                      |                                     |                          |                          |
| Elementary school with vocational school or below | 58 (95.08) | 54 (91.52) | 56 (93.33) | 168 (93.33) |
| Junior high and above             | 3 (4.92)                             | 5 (8.47)                            | 4 (6.67)                  | 12 (6.67)                 |
| Annual income Euro, median, (IQR) | 8,074 (4,878, 13,036)                 | 7,569 (5,382, 12,111)               | 7,401 (4,962, 11,606)     | 7,569 (5,046, 12,111)     |
| Marital status, married, n (%)    | 51 (83.61)                           | 52 (88.14)                          | 51 (85.00)                | 154 (85.56)               |
| BMi, median, (IQR)                | 27.16 (26.01, 30.74)                 | 27.53 (25.83, 29.25)                | 29.95 (27.04, 31.88)      | 28.17 (26.09, 30.63)      |
| Family history of CVD, n (%)      | 55 (90.16)                           | 54 (91.53)                          | 57 (95.00)                | 166 (92.22)               |
| Currently taking medications, n (%) |                                     |                                     |                          |                          |
| Hypertensives                     | 45 (73.77)                           | 40 (67.80)                          | 41 (68.33)                | 126 (70.00)               |
| Diuretics                         | 19 (31.15)                           | 17 (28.81)                          | 26 (43.33)                | 62 (34.44)                |
| High cholesterol                  | 1 (1.64)                             | 1 (1.69)                            | 1 (1.67)                  | 3 (1.67)                  |
| Beta blocking agents              | 39 (64.00)                           | 37 (62.71)                          | 31 (51.67)                | 107 (59.44)               |
| Diuretics, class, n (%)           |                                      |                                     |                          |                          |
| Hydrochlorothiazide and potassium-sparing agents | 1 (1.64) * | 5 (8.47) * | 2 (3.33) * | 8 (4.44)* |
| Hydrochlorothiazide               | –                                    | –                                   | 3 (5.00)*                 | 3 (1.67)*                 |
| Furosemide and potassium-sparing agents | 1 (1.64)* | – | 2 (3.33)* | 3 (1.67)* |
| Furosemide                        | 1 (1.64)*                            | 1 (1.69)                            | 3 (5.00)*                 | 5 (2.78)*                 |
| Triamterene                       | –                                    | 1 (1.69)                            | 1 (0.56)                  | –                         |
| Medical conditions, n (%)         |                                      |                                     |                          |                          |
| Diabetes (T1DM and T2DM)          | 9 (14.75)                            | 7 (11.86)                           | 11 (18.33)                | 27 (15.00)                |
| Hypertension                      | 45 (75.00)                           | 38 (65.52)                          | 33 (56.90)                | 116 (65.91)               |

BMI = body mass index, CVD = cardiovascular disease, T1DM = type-1 diabetes mellitus, T2DM = type-2 diabetes mellitus

*42 missing values
In unadjusted models, relative to tertile 1, those in tertile 2 and 3 were 32% (HR 0.68; 95% CIs 0.43, 1.05) and 27% less likely to have a MACE event (HR 0.73; 95% CIs 0.46, 1.14), respectively however neither association was statistically significant (Table 2).

Table 3 shows the magnitude of these associations after adjustment for covariates. The trend between tertile 1 and 2 observed in the unadjusted model was lost when adjusted for age and full adjustment for age, smoking, beta blocking agents, diabetes, and mean diastolic blood pressure. Kaplan–Meier survival estimates displayed in Fig. 2A demonstrated the extent to which \( U_{Na} \) groups diverged over the analysis period with respect to time to MACE. Tertile 2 in comparison to Tertile 1 was non-significant with time to MACE events at commencement and a subsequent convergence after year 30 of follow up. Tertile 3 compared to tertile 1 until year 22 was noted to have a higher survival rate, following which, the survival time converged for tertiles 1 and 3. Figure 2B provides model-adjusted time to MACE for the final model.

### Urinary sodium excretion and all-cause mortality

One hundred and fifty all-cause deaths were recorded over median 19 (IQR 9, 28) years with \( n = 54, 46, \) and \( 50 \) MACE events across tertiles 1, 2, and 3 respectively (Table 4). The rate of event per 1000 person years was 54.16, 36.29, and 48.10, across tertiles 1, 2, and 3 respectively, with the lowest MACE events observed in tertile 2. In unadjusted models, relative to tertile 1, those in tertile 2 were 39% less likely to experience all-cause mortality over the follow up period (HR: 0.61; 95% CIs: 0.41, 0.91), and significance remained following adjustment for beta blocking agents, income, age, smoking, BMI, and diabetes. The multivariable Cox model had acceptable prediction precision as measured by Harrell’s C concordance statistic (Harrell’s \( C = 0.72 \)). Those in tertile 3 were 10% less likely to experience all-cause mortality (HR 0.90; 95% CIs 0.62, 1.33), although this comparison was not significant (Table 5).

MFP was used to investigate curvature in urinary sodium when included as a continuous exposure in the multivariable Cox model (Additional file 2: Tables S1 and S2). While the model showed an improvement in model goodness of fit the fractional polynomial term was not statistically significant (\( p\)-value = 0.185).

### Discussion

This study is the first of its kind to use long-term, prospective data to assess the relationship between \( U_{Na} \) and MACE as well as all-cause mortality outcomes in men with HF. Our data indicates \( U_{Na} \) is may be of prognostic value regarding all-cause mortality but less so for MACE. This association appeared to be U-shaped in nature, which has been previously seen \( U_{Na} \) and MACE events [15] as well as for incident heart failure [16].
An explanation for a lack of association between $U_{Na}$ and MACE outcomes in this study could be due to type 1 error owing to a lack of statistical power due to the limited number of events in the KIHD cohort. A significant association was observed between $U_{Na}$ and all-cause mortality events for which there were a greater number
of events. Indeed, those with \( U_{Na} \) of 173–229 mmol/day had the lowest likelihood of all-cause mortality suggesting thereby suggesting there may be an optimal \( U_{Na} \) target for the purpose of self-management. Our study, provides a rationale for further investigation of its prognostic accuracy in a larger, more inclusive sample.

The potential prognostic value of \( U_{Na} \) is corroborated by the literature from acute decompensated HF. Low \( U_{Na} \) has a strong correlation with poor prognosis for hospitalised patients and increased length of stay [7, 17]. It is thought to be associated with HF due to reduced ejection fraction resulting in compensatory upregulation of the renin angiotensin system [18]. Furthermore, poor response to diuretic therapy in patients with HF is associated with a worse prognosis [16]. On the other hand, high \( U_{Na} \) is a reflection of dietary sodium intake, which correlates with a greater risk of developing HF [19]. Recommendations from current guidelines globally on daily salt intake in HF patients vary significantly, potentially due to lack of conclusive evidence [20–22]. However, emerging literature reveal a paradoxical association between low dietary sodium and a worse HF prognosis [23]. Due to the ambiguity of the role of dietary sodium, a large multi-centre randomised control trial (SODIUM-HF) is currently in progress aiming to elucidate the effect of dietary sodium < 1500 mg per day compared to current HF guideline dietary recommendations [24].

While there was a general U shaped trend noted in our study, this finding is not widely reflected in the literature. Martens and colleagues noted an inverse relationship between urinary sodium and risk of acute decompensation in patients with stable HF at baseline [25]. This variation in results could be due to the outcome measure; our study assessed MACE, in lieu of acute decompensation events. Furthermore, as the participants enrolled had a prior diagnosis of HF, they may have received dietary education at the time of initial diagnosis.

Another explanation could be dosing and compliance with HF pharmacotherapy which was not assessed. Diuretics, regardless of their class, exert their effect by increasing excretion of sodium and therefore water [26]. Dose reduction, possibly as a consequence of haemodynamic instability or acute biochemical marker derangements in addition to non-adherence with this class of medication can give rise to skewed results. In the KIHD cohort, 34.44% of participants at baseline were prescribed diuretics, however, with the limited data available summarising diuretics class (Table 1), no conclusions can be drawn regarding the effects of individual classes on MACE outcomes. Whilst evidence indicates that poor-response to diuretic use is associated with a worse HF prognosis, there are limited data on mortality benefit with certain types of diuretics. More specifically, loop diuretics haven’t been shown to

| Table 4 | All-cause mortality rates (n/1000), and unadjusted HR for tertiles of urinary sodium excretion with their 95% confidence interval |
|---------|---------------------------------------------------------------|
| Tertile 1 (< 173 mmol/day) | Tertile 2 (173–229 mmol/day) | Tertile 3 (230–491 mmol/day) |
| (n = 61) | (n = 59) | (n = 60) |
| Median survival analysis time (years) [IQR] | 10.3 years [3.6–20.9] | 14.3 years [7.5–27.2] | 12.8 years [12.8–21.4] |
| All-cause mortality | 54 | 46 | 50 |
| total follow-up (1000 person years) | 1.00 | 1.27 | 1.04 |
| Rate (per 1000 person years) | 54.16 (41.48, 70.71) | 36.29 (27.18, 48.45) | 48.10 (36.45, 63.46) |
| Unadjusted HR | REF | 0.61 (0.41, 0.91) | 0.90 (0.62, 1.33) |
| P value | REF | 0.014 | 0.609 |

| Table 5 | Cox survival analysis: Hazard ratio (HR) and 95% confidence interval of all-cause mortality rate across tertiles of urinary sodium excretion |
|---------|---------------------------------------------------------------|
| Urinary sodium excretion | HR | 95%CI | Chi² | p value |
| Model 1 | | | | |
| Tertile 1 | 1.00 | Reference | | |
| Tertile 2 | 0.61 | 0.41, 0.91 | 6.51 | 0.04 |
| Tertile 3 | 0.90 | 0.62, 1.33 | | |
| Model 2 | | | | |
| Tertile 1 | 1.00 | Reference | | |
| Tertile 2 | 0.62 | 0.42, 0.92 | 6.57 | 0.04 |
| Tertile 3 | 0.96 | 0.65, 1.42 | | |
| Model 3 | | | | |
| Tertile 1 | 1.00 | Reference | | |
| Tertile 2 | 0.61 | 0.40, 0.91 | 6.57 | 0.04 |
| Tertile 3 | 0.93 | 0.61, 1.42 | | |

* Model adjusted for age, model adjusted for beta blocking agents, income, age, smoking, BMI, and diabetes, tertile 1 < 173 mmol/day, tertile 2 = 173–229 mmol/day, tertile 3 = 230–491 mmol/day, d.f. = 2, Chi² results are from testing of Cox regression beta coefficients.
confer long-term prognostic benefit in HF [27]. As we were underpowered to conduct meaningful analyses by sub-class of diuretics and anti-hypertensive agents taken by participants, future research investigating the link between sodium and MACE outcomes in HF patients will likely benefit from a detailed assessment of both these classes of medications in order to tease out potential effects of individual classes.

All-cause mortality was also noted to have a U shape association with \( U_{Na} \) which is similar to the trend noted with MACE events. This could be a consequence of higher and lower \( U_{Na} \) having poor control of comorbidities such as respiratory diseases, renal disease and malignancy which is known to contribute significantly toward non-cardiac mortality in patients with HF [28]. Due to the limited participant baseline screening data, it is difficult to elucidate the mechanism by which all-cause mortality is associated with \( U_{Na} \).

If these findings are replicated in a larger, more diverse sample, there may be implications for clinical practice with respect to the management of sodium intake in patients with HF. Evidence-based, best practice for managing HF with reduced ejection fraction (HFrEF) includes pharmacotherapy; angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blocker (ARB), beta-blockers, mineralocorticoid receptor antagonists (MRAs), angiotensin receptor-neprilysin inhibitor (ARNI), hydralazine, nitrates and omega 3 polyunsaturated fatty acids. More recent evidence also supports the beneficial role of sodium glucose co-transporter type 2 (SGLT-2) inhibitors in reducing cardiovascular death rate and HF associated hospitalisation [29, 30]. While this therapeutic approach can help manage symptoms, prolong survival and improve quality of life (QoL) [21], morbidity and mortality remains high despite optimal therapy [31]. The PARADIGM-HF study showed that CHF patients receiving optimal therapy still had a 23% chance of cardiovascular death or CHF hospitalisation over the next 27 months [32]. In contrast, optimal management for heart failure with preserved ejection fraction (HFpEF) is not well understood. With the exception of MRAs and more recently SGLT-2 inhibitors, there is no clear evidence to support use of ACE/ARB, beta blockers, ARNI, calcium channel blockers and nitrates [33, 34]. This could be attributed to the various causes of HFpEF; the lack of etiological homogeneity preventing a clear consensus on prognostically beneficial pharmacotherapy. In light of this and our findings, dietary interventions may provide a safe, attractive approach to self-management of HF while encouraging adequate nutrition in patients whose condition can cause nutrient deficiencies and would benefit from further investigation. There is, however, a dearth of efficacy or acceptability data on dietary interventions in HF populations. US, Australian and European guidelines highlighted significant gaps in this area [21] and there remain no evidence-based recommendations beyond expert opinion.

**Limitations**

This study focuses on an area of HF management with a relatively limited evidence base. It provides long-term longitudinal data pertaining to \( U_{Na} \) in HF patients, measured using gold standard 24 h urine collection. However, the relatively small sample size may have contributed to the association between \( U_{Na} \) and MACE being attenuated. Secondly, the external validity of this study may be limited by the homogeneity of the participants, given recruitment was limited to Eastern Finnish men and therefore these findings cannot be generalized to females. Furthermore, participant’s dietary sodium intake was not measured. Diuretic agents were also not withheld during baseline and subsequent \( U_{Na} \) measurement which may have resulted a left skew in the measured \( U_{Na} \). The MACE outcomes could not be stratified based on current HF directed therapy and anti-hyperglycaemic agents owing to limited data available pertaining to the class of diuretics and anti-hypertensive agents in the KIHD cohort. Due to the variation in the median follow up across the urinary tertile groups, there may exist time in survival analysis bias. Lastly, as the urinary sodium was held constant for analysis of confounders, they may be factors dependent on the real time variability of urinary sodium that may not have been accounted.

**Conclusion**

The current study suggests that further investigation of the long-term, prognostic value of 24 h \( U_{Na} \) may be warranted in HF patients. Future research in this area would benefit from the inclusion of detailed medication classes and the inclusion of a large number of patients, representative of the wider patient population, including women and other ethnic groups, with characterisation of HF sub-type.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s12872-022-02830-3.
Table 5: Model prediction with and without inclusion of urinary tertiles

Sup. Table 4: Joint association of urinary sodium and potassium excretion with cardiovascular events and mortality: prospective cohort study. bmj. 2019;364:l444.

Pfister R, Michels G, Sharp SJ, Luben R, Wareham NJ, Khaw KT. Estimated urinary sodium excretion and risk of heart failure in men and women in the EPIC-Norfolk study. Eur J Heart Fail. 2014;16:394–402.

Ferreira JP, Gierd N, Medeiros PB, Santos M, Carvalho HC, Bettencourt P, Kénizou D, Butler J, Zannad F, Rossignol P. Spot urine sodium excretion as prognostic marker in acutely decompensated heart failure: the spironolactone effect. Clin Res Cardiol. 2016;105:489–507.

Zucker IH, Xiao L, Haack KK. The central renin-angiotensin system and sympathetic nerve activity in chronic heart failure. Clin Sci. 2014;126:695–706.

Kagayama S, Koga T, Kaseda S, Ishihara S, Kawazoe N, Sadoshima S, Matsumura K, Takata Y, Tsuchihashi T, Iida M. Correlation between increased urinary sodium excretion and decreased left ventricular diastolic function in patients with type 2 diabetes mellitus. Clin Cardiol Int Index Peer-Rev J Adv Treat Cardiovasc Dis. 2009;32:569–74.

Hummel SL, Konerman MC. Dietary sodium restriction in heart failure: a recommendation worth its salt? JACC Heart Fail. 2016. https://doi.org/10.1016/j.jchf.2015.10.003.

Atherton JI, Sindone A, De Pasquale CG, Driscoll A, MacDonald PS, Hopper I, Kistler PM, Briffa T, Wong J, Abhayaratna W. National heart foundation of Australia and cardiac society of Australia and New Zealand:
guidelines for the prevention, detection, and management of heart failure in Australia 2018. Heart Lung Circ. 2018;27:1123–208.

22. Gupta D, Georgiopoulou VV, Kalogeropoulos AP, Dunbar SB, Reilly CM, Sands JM, Fonarow GC, Jessup M, Gheorghiade M, Yancy C. Dietary sodium intake in heart failure. Circulation. 2012;126:479–85.

23. Khan MS, Jones DW, Butler J. Salt, no salt, or less salt for patients with heart failure? Am J Med. 2020;133:32–8.

24. Colin-Ramirez E, Ezekowitz JA. Rationale and design of the study of dietary intervention under 100 MMOL in heart failure (SODIUM-HF). Am Heart J. 2018;205:87–96.

25. Martens P, Dupont M, Verbrugge FH, Damman K, Degryse N, Nijst P, Reynolds C, Penders J, Tang WW, Testani J. Urinary sodium profiling in chronic heart failure to detect development of acute decompensated heart failure. JACC Heart Fail. 2019;7:404–14.

26. Casu G, Merella P. Diuretic Therapy in heart failure—current approaches. European Cardiology Review. 2015;10:42.

27. Kapelios CJ, Malliaras K, Kalda E, Vakrou S, Nanas JN. Loop diuretics for chronic heart failure: a foe in disguise of a friend? European Heart J Cardiovasc Pharmacother. 2018;4:54–63.

28. Vergaro G, Ghionzoli N, Innocenti L, Taddei C, Giannoni A, Valleggi A, Borrelli C, Senni M, Passino C, Emdin M. Noncardiac versus cardiac mortality in heart failure with preserved, midrange, and reduced ejection fraction. J Am Heart Assoc. 2019;8: e013441.

29. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-reduced and DAPA-HF trials. Lancet. 2020. https://doi.org/10.1016/S0140-6736(20)31824-9.

30. Seferovic PM, Coats AJ, Ponikowski P, Filippatos G, Huelsmann M, Jhund PS, Polovina MM, Komajda M, Seferovic J, Sari I. European society of cardiology/heart failure association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. Eur J Heart Fail. 2020;22:196–213.

31. Ferrin PC, McCreath L, Navankasattusas S, Drakos SG. Recovery versus remission: clinical insights. Heart Fail Clin. 2016;12:449–59.

32. Okumura N, Jhund PS, Gong J, Lefkowitz MR, Rozala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Solomon SD. Effects of sacubitril/valsartan in the PARADIGM-HF trial (prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure) according to background therapy. Circ Heart Fail. 2016;9:e003212.

33. Henning RJ. Diagnosis and treatment of heart failure with preserved left ventricular ejection fraction. World J Cardiol. 2020;12:7–25.

34. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chiquiure-Valenzuela E. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385:1451–61.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.