Sacubitril/valsartan reduces serum uric acid concentration, an independent predictor of adverse outcomes in PARADIGM-HF

Mogensen, Ulrik M.; Køber, Lars; Jhund, Pardeep S.; Desai, Akshay S.; Senni, Michele; Kristensen, Søren L.; Dukát, Andrej; Chen, Chen Huan; Ramires, Felix; Lefkowitz, Martin P.; Prescott, Margaret F.; Shi, Victor C.; Rouleau, Jean L.; Solomon, Scott D.; Swedberg, Karl; Packer, Milton; Mcmurray, John J.V.

Published in:
European Journal of Heart Failure

DOI:
10.1002/ejhf.1056

Publication date:
2018

Document version
Publisher's PDF, also known as Version of record

Document license:
CC BY-NC

Citation for published version (APA):
Mogensen, U. M., Køber, L., Jhund, P. S., Desai, A. S., Senni, M., Kristensen, S. L., ... Mcmurray, J. J. V. (2018). Sacubitril/valsartan reduces serum uric acid concentration, an independent predictor of adverse outcomes in PARADIGM-HF. European Journal of Heart Failure, 20(3), 514-522. https://doi.org/10.1002/ejhf.1056
Sacubitril/valsartan reduces serum uric acid concentration, an independent predictor of adverse outcomes in PARADIGM-HF

Ulrik M. Mogensen1,2, Lars Køber2, Pardeep S. Jhund1, Akshay S. Desai3, Michele Senni4, Søren L. Kristensen1,2, Andrej Dukát5, Chen-Huan Chen6, Felix Ramires7, Martin P. Lefkowitz8, Margaret F. Prescott8, Victor C. Shi8, Jean L. Rouleau9, Scott D. Solomon3, Karl Swedberg10, Milton Packer11, and John J.V. McMurray1*, on behalf of the PARADIGM-HF Investigators and Committees†

1BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; 2Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; 3Cardiovascular Medicine, Brigham and Women’s Hospital, Boston, MA, USA; 4Cardiology, Heart Failure and Heart Transplant Unit, Hospital Papa Giovanni XXIII, Bergamo, Italy; 5Second Department of Internal Medicine, Comenius University, Bratislava, Slovakia; 6Department of Medicine, National Yang-Ming University, Republic of China, Department of Medical Education, Taipei Veterans General Hospital, Taipei, Taiwan, Republic of China; 7Heart Institute (InCor) – University of São Paulo, Medical School, Brazil; 8Novartis Pharmaceutical Corporation, East Hanover, NJ, USA; 9Institut de Cardiologie, Université de Montréal, Montréal, Canada; 10Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden and National Heart and Lung Institute, Imperial College London, London, UK; and 11Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, TX, USA

Received 4 June 2017; revised 28 July 2017; accepted 11 August 2017; online publish-ahead-of-print 30 November 2017

Aims

Elevated serum uric acid concentration (SUA) has been associated with an increased risk of cardiovascular disease, but this may be due to unmeasured confounders. We examined the association between SUA and outcomes as well as the effect of sacubitril/valsartan on SUA in patients with heart failure with reduced ejection fraction (HFrEF) in PARADIGM-HF.

Methods and results

The association between SUA and the primary composite outcome of cardiovascular death or heart failure (HF) hospitalization, its components, and all-cause mortality was examined using Cox regression analyses among 8213 patients using quintiles (Q1–Q5) of SUA adjusted for baseline prognostic variables including estimated glomerular filtration rate (eGFR), diuretic dose, and log N-terminal pro-brain natriuretic peptide. Change in SUA from baseline over 12 months was also evaluated in each treatment group. Patients in Q5 (SUA ≥8.6 mg/dL) compared with Q1 (<5.4 mg/dL) were younger (62.8 vs. 64.2 years), more often male (88.7% vs. 63.1%), had lower systolic blood pressure (119 vs. 123 mmHg), lower eGFR (57.4 vs. 76.6 mL/min/1.73 m²), and greater diuretic use. Higher SUA was associated with a higher risk of the primary outcome (adjusted hazard ratios) Q5 vs. Q1 = 1.28 [95% confidence intervals (1.09–1.50), P = 0.003], cardiovascular death [1.44 (1.11–1.77), P = 0.001], HF hospitalization [1.37 (1.11–1.70), P = 0.004], and all-cause mortality [1.36 (1.13–1.64), P = 0.001]. Compared with enalapril, sacubitril/valsartan reduced SUA by 0.24 (0.17–0.32) mg/dL over 12 months (P < 0.0001). Sacubitril/valsartan improved outcomes, irrespective of SUA concentration.

Conclusion

Serum uric acid concentration was an independent predictor of worse outcomes after multivariable adjustment in patients with HFrEF. Compared with enalapril, sacubitril/valsartan reduced SUA and improved outcomes irrespective of SUA.

Keywords

Heart failure • Uric acid • Mortality • Neprilysin • Angiotensin

© 2017 The Authors. European Journal of Heart Failure published by John Wiley & Sons Ltd on behalf of European Society of Cardiology. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
Introduction

Uric acid (UA) is the final product of purine metabolism and the serum concentration of UA (SUA) reflects the balance between dietary intake of purines, the synthesis of UA by xanthine oxidase (along with superoxide) and UA excretion, principally by the kidneys but also through the gastrointestinal tract. Diuretic treatment is also associated with high SUA, probably because diuretics impair UA excretion.

As well as potentially reflecting oxidative stress as a consequence of xanthine oxidase activity, UA may itself have harmful effects such as increasing expression of cytokines and chemokines, inducing inflammation, impairing endothelial function and activating the renin–angiotensin system.

Hyperuricemia is common in many forms of cardiovascular disease, including heart failure (HF). In patients with acute and chronic HF, higher SUA is associated with worse clinical outcomes. Whether SUA is an independent predictor of outcome is less certain as renal function and use of diuretics (and diuretic dose) has been variably adjusted for. Additionally, only one prior study has adjusted for natriuretic peptide levels and that was a study in acute HF.

The effect of treatments for HF on UA concentration is also of interest and UA lowering agents have been investigated as a potential therapy for HF. We have, therefore, examined the predictive value of SUA in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) and determined the effect of sacubitril/valsartan (formerly known as LCZ696) on SUA.

Methods

Patients and procedures

The design and primary results of PARADIGM-HF have been reported previously. Briefly, PARADIGM-HF was a randomized, double-blinded comparison of the ARNI sacubitril/valsartan with enalapril in patients with chronic HF with reduced ejection fraction (HFrEF). Eligibility criteria at screening included New York Heart Association (NYHA) classes II–IV, left ventricular ejection fraction (LVEF) ≤ 40% (changed to ≤35% by amendment), and elevated natriuretic peptides. Exclusion criteria at screening included symptomatic hypotension or systolic blood pressure < 100 mmHg, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m², and potassium > 5.2 mmol/L.

On trial entry, ongoing therapy with angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) was stopped and patients entered sequential run-in, first receiving enalapril 10 mg b.i.d. for 2 weeks followed by sacubitril/valsartan for additional 4–6 weeks up titrated from 100 mg to 200 mg b.i.d. Patients tolerating both drugs at these target doses were randomly assigned to double-blinded therapy with sacubitril/valsartan or enalapril in a 1:1 ratio.

Measurement of SUA was performed at screening, during run-in (when changing from enalapril to sacubitril/valsartan), at randomization, and after 2, 4, and 12 months of follow-up and yearly thereafter. Evaluations of SUA were performed through a central laboratory. SUA was converted from μmol/L to mg/dL by division with 59.48. The upper limit of normal for the SUA assay used was 8.0 mg/dL for men and 7.3 mg/dL for women aged 66–90 years, and 6.9 mg/dL for women aged 18–65 years.

Outcomes

The primary endpoint in PARADIGM-HF was a composite of cardiovascular death and HF hospitalization. In this study, we investigated the association between SUA and the risk of the primary outcome, each of its components, and all-cause mortality. All endpoints were adjudicated by a clinical endpoint committee in a blinded fashion. We also compared the effects of the randomized treatment on SUA 4, 12, and 24 months after randomization, as described below.

Statistical analyses

Baseline characteristics are presented as frequencies and percentages for categorical variables and means with standard deviation or medians with interquartile range for continuous variables. Differences in baseline characteristics were tested using χ² test for categorical variables and analysis of variance (ANOVA) or Kruskal–Wallis test for continuous variables. Use of loop diuretics at baseline was grouped in categories of furosemide equivalents: 40 mg furosemide = 20 mg torsemide = 1 mg bumetanide. Non-loop diuretics (primarily thiazide and indapamide) were categorized as ‘other’.

Incidence rates for each outcome of interest are presented per 100 person years of follow-up. Event rates in each SUA quintile were estimated by the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression models were used to compare hazard ratios (HRs) with 95% confidence intervals (CIs) according to SUA quintiles. In multivariable models, the HR was adjusted for the following baseline characteristics: age, sex, race, region, systolic blood pressure, heart rate, ejection fraction, NYHA class, history of HF hospitalization, duration of HF, atrial fibrillation, diabetes, body mass index, prior myocardial infarction, prior stroke, eGFR, haemoglobin, sodium, albumin, randomized treatment (sacubitril/valsartan), diuretic dose, and log transformed N-terminal pro brain natriuretic peptide (NT-proBNP).

The association between SUA and each outcome was also assessed in an adjusted model using a restricted cubic spline with five knots using SUA of 7.0 mg/dL as reference. For the risk of each of the outcomes, there were no interactions between SUA levels and sex. The proportional hazards assumption was evaluated using plots of Schoenfeld residuals vs. log time and found valid, as was the assumption of linearity of continuous variables.

Changes in SUA were assessed by repeated measures mixed model with the baseline score as a covariate, and treatment, region, time, and treatment by time interaction as fixed effects, with a common unstructured covariance for each treatment group.

Analyses were performed using Stata version 13 (Stata Corp., College Station, TX, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All P-values are two-sided, and a P-value < 0.05 was considered significant.

Results

Of the 8399 patients randomized, 8213 had a SUA measurement at randomization. Mean SUA was 6.9 ± 2.0 mg/dL, 7.1 ± 2.0 mg/dL in men and 6.1 ± 1.8 mg/dL in women (P < 0.001) (distributions of SUA overall and according to sex and region are illustrated in the supplementary material online, Figures S1 and S2).
### Table 1 Baseline characteristics

| Serum uric acid concentration at randomization | P-value |
|-----------------------------------------------|---------|
| Q1 (n = 1635) | Q2 (n = 1616) | Q3 (n = 1688) | Q4 (n = 1643) | Q5 (n = 1551) |
|----------------|----------------|---------------|---------------|---------------|
| Serum uric acid (mg/dL), mean ± SD | 4.4 ± 0.7 | 5.8 ± 0.3 | 6.7 ± 0.3 | 7.9 ± 0.4 | 9.2 ± 1.2 |
| mg/dL, range | 0.3–5.3 | 5.4–6.2 | 6.3–7.2 | 7.3–8.5 | 8.6–17.1 |
| Age at screening (years) | 64.16 ± 11.19 | 64.00 ± 10.98 | 64.21 ± 11.25 | 63.61 ± 11.65 | 62.83 ± 11.84 |
| Female sex | 603 (36.9%) | 427 (25.2%) | 338 (20.0%) | 250 (15.2%) | 176 (11.3%) |
| Randomized to sacubitril/valsartan | 802 (49.1%) | 849 (50.1%) | 825 (48.9%) | 831 (50.6%) | 785 (50.6%) |
| Region | <0.001 |
| North America | 92 (5.6%) | 98 (5.8%) | 128 (7.6%) | 129 (7.9%) | 141 (9.1%) |
| Latin America | 342 (20.9%) | 302 (17.8%) | 276 (16.4%) | 280 (17.0%) | 211 (13.6%) |
| Western Europe | 282 (17.2%) | 360 (21.2%) | 432 (25.6%) | 427 (26.0%) | 484 (31.2%) |
| Central Europe | 640 (39.1%) | 617 (36.4%) | 579 (34.3%) | 496 (30.2%) | 419 (27.0%) |
| Asia/Pacific and other | 279 (17.1%) | 319 (18.8%) | 273 (16.2%) | 311 (18.9%) | 296 (19.1%) |
| Race | <0.001 |
| White | 1080 (66.1%) | 1102 (65.0%) | 1148 (68.0%) | 1064 (64.8%) | 999 (64.4%) |
| Black | 70 (4.3%) | 76 (4.5%) | 82 (4.9%) | 92 (5.6%) | 102 (6.6%) |
| Other | 272 (16.6%) | 324 (19.1%) | 280 (16.6%) | 317 (19.3%) | 308 (19.9%) |
| Systolic blood pressure (mmHg) | 123.38 ± 15.04 | 123.03 ± 15.79 | 121.10 ± 15.43 | 120.40 ± 14.73 | 118.55 ± 14.94 |
| Heart rate (b.p.m.) | 72.13 ± 11.28 | 72.05 ± 11.79 | 71.81 ± 12.07 | 72.56 ± 12.22 | 73.45 ± 12.79 |
| eGFR (mL/min/1.73 m²) | 76.61 ± 21.67 | 71.82 ± 19.08 | 67.81 ± 18.10 | 64.22 ± 18.17 | 57.38 ± 18.05 |
| Serum creatinine (µmol/L) | 84.95 ± 21.88 | 92.27 ± 22.34 | 98.06 ± 22.96 | 104.79 ± 24.22 | 117.83 ± 28.20 |
| Ischaemic HF aetiology | 1007 (61.6%) | 1001 (59.0%) | 1021 (60.5%) | 983 (59.8%) | 900 (58.0%) |
| Ejection fraction (%) | 29.98 ± 6.03 | 29.93 ± 6.06 | 29.57 ± 6.17 | 29.22 ± 6.33 | 28.63 ± 6.37 |
| NYHA class | <0.001 |
| I | 66 (4.0%) | 82 (4.8%) | 76 (4.5%) | 82 (5.0%) | 77 (5.0%) |
| II | 1164 (71.2%) | 1209 (71.3%) | 1210 (71.7%) | 1191 (72.5%) | 1016 (65.5%) |
| III | 391 (23.9%) | 390 (23.0%) | 388 (23.0%) | 363 (22.1%) | 436 (28.1%) |
| IV | 13 (0.8%) | 14 (0.8%) | 10 (0.6%) | 6 (0.4%) | 16 (1.0%) |
| Duration of HF | <0.001 |
| ≤1 year | 553 (33.8%) | 537 (31.7%) | 503 (29.8%) | 468 (28.5%) | 417 (26.9%) |
| 1–5 years | 597 (36.5%) | 682 (40.2%) | 644 (38.2%) | 644 (39.2%) | 605 (39.0%) |
| >5 years | 485 (29.7%) | 477 (28.1%) | 541 (32.0%) | 531 (32.3%) | 529 (34.1%) |
| A history of | <0.001 |
| Hypertension | 1152 (70.5%) | 1216 (71.7%) | 1191 (70.6%) | 1158 (70.5%) | 1084 (69.9%) |
| Diabetes | 555 (33.9%) | 570 (33.6%) | 577 (34.2%) | 562 (34.2%) | 579 (37.3%) |
| Myocardial infarction | 704 (43.1%) | 689 (40.6%) | 761 (45.1%) | 718 (43.7%) | 666 (42.9%) |
| Valvular heart disease | 98 (6.0%) | 116 (6.8%) | 128 (7.6%) | 114 (6.9%) | 136 (8.8%) |
| Atrial fibrillation | 507 (31.0%) | 551 (32.5%) | 608 (36.0%) | 661 (40.2%) | 688 (44.4%) |
| HF hospitalization | 958 (58.6%) | 1009 (59.5%) | 1055 (62.5%) | 1060 (64.5%) | 1080 (69.6%) |
| Stroke | 138 (8.4%) | 132 (7.8%) | 138 (8.2%) | 148 (9.0%) | 152 (9.8%) |
| COPD | 182 (11.1%) | 202 (11.9%) | 213 (12.6%) | 239 (14.5%) | 218 (14.1%) |
| Cancer | 83 (5.1%) | 81 (4.8%) | 80 (4.7%) | 85 (5.2%) | 72 (4.6%) |
| Medications | <0.001 |
| Beta-blocker | 1516 (92.7%) | 1578 (93.0%) | 1571 (93.1%) | 1537 (93.5%) | 1439 (92.8%) |
| Mineralocorticoid receptor antagonist | 849 (51.9%) | 889 (52.4%) | 947 (56.1%) | 967 (58.9%) | 926 (59.7%) |
| Diogxin | 409 (25.0%) | 493 (29.1%) | 496 (29.4%) | 549 (33.4%) | 543 (35.0%) |
| Diuretics | <0.001 |
| Loop diuretic (<40 mg) | 450 (27.5%) | 492 (29.0%) | 495 (29.3%) | 459 (27.9%) | 355 (22.9%) |
| Loop diuretic (40–80 mg) | 449 (27.5%) | 482 (28.4%) | 528 (31.3%) | 537 (32.7%) | 551 (35.5%) |
| Loop diuretic (>80 mg) | 174 (10.6%) | 215 (12.7%) | 231 (13.7%) | 296 (18.0%) | 437 (28.2%) |
| Other | 97 (5.9%) | 100 (5.9%) | 87 (5.2%) | 89 (5.4%) | 49 (3.2%) |
### Table 1

| Uric acid lowering drugs | Q1 (n = 1635) | Q2 (n = 1696) | Q3 (n = 1688) | Q4 (n = 1643) | Q5 (n = 1551) | P-value |
|--------------------------|---------------|---------------|---------------|---------------|---------------|---------|
| None                     | 1440 (88.1%)  | 1521 (89.7%)  | 1525 (90.3%)  | 1471 (89.5%)  | 1411 (91.0%)  | 0.082   |
| Allopurinol              | 188 (11.5%)   | 167 (9.8%)    | 159 (9.4%)    | 169 (10.3%)   | 134 (8.6%)    |         |
| Febuxostat               | 5 (0.3%)      | 6 (0.4%)      | 0 (0.0%)      | 1 (0.1%)      | 2 (0.1%)      |         |
| Benzbromarone            | 2 (0.1%)      | 2 (0.1%)      | 4 (0.2%)      | 1 (0.1%)      | 4 (0.3%)      |         |
| Sulfipyrazole            | 0 (0.0%)      | 0 (0.0%)      | 0 (0.0%)      | 1 (0.1%)      | 0 (0.0%)      |         |

Laboratory values at randomization

| | Q1 | Q2 | Q3 | Q4 | Q5 |
|---|---|---|---|---|---|
| Sodium (mmol/L) | 138.8 ± 15.20 | 138.84 ± 15.66 | 139.86 ± 15.48 | 140.71 ± 16.42 | 140.06 ± 17.09 |
| Albumin (g/L) | 42.71 ± 3.08 | 42.71 ± 3.09 | 42.80 ± 3.14 | 42.76 ± 3.16 | 42.93 ± 3.29 |
| Haemoglobin (g/L) | 137.31 ± 15.10 | 138.84 ± 15.66 | 139.86 ± 15.48 | 140.71 ± 16.42 | 140.06 ± 17.09 |
| Albumin (g/L) | 42.71 ± 3.08 | 42.71 ± 3.09 | 42.80 ± 3.14 | 42.76 ± 3.16 | 42.93 ± 3.29 |

Data are numbers (proportion), mean ± standard deviation, and median (interquartile range), as appropriate.

BNP: brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; Q, quintile.

### Table 2

| No. events | Crude rate per 100 PY | Unadjusted HR (95% CI) | P-value | Adjusted HR* (95% CI) | P-value |
|------------|-----------------------|------------------------|---------|-----------------------|---------|
| Primary composite |
| Q1: <5.4 mg/dL | 320 | 9.3 (8.3–10.4) | 1.00 (reference) | 1.00 (reference) |         |
| Q2: 5.4–6.2 mg/dL | 352 | 9.8 (8.8–10.9) | 1.05 (0.91–1.23) | 0.49 | 1.00 (0.85–1.16) | 0.97 |
| Q3: 6.3–7.2 mg/dL | 382 | 10.8 (9.8–12) | 1.17 (1.01–1.35) | 0.042 | 1.03 (0.88–1.20) | 0.71 |
| Q4: 7.3–8.5 mg/dL | 415 | 12.5 (11.3–13.8) | 1.34 (1.16–1.55) | <0.001 | 1.07 (0.92–1.25) | 0.37 |
| Q5: ≥8.6 mg/dL | 518 | 17.9 (16.4–19.5) | 1.91 (1.66–2.19) | <0.001 | 1.28 (1.09–1.50) | 0.003 |
| CV death |
| Q1: <5.4 mg/dL | 191 | 5.2 (4.5–6) | 1.00 (reference) | 1.00 (reference) |         |
| Q2: 5.4–6.2 mg/dL | 229 | 6.0 (5.3–6.9) | 1.15 (0.95–1.4) | 0.14 | 1.11 (0.91–1.35) | 0.29 |
| Q3: 6.3–7.2 mg/dL | 226 | 6.0 (5.2–6.8) | 1.14 (0.94–1.39) | 0.18 | 1.04 (0.85–1.27) | 0.70 |
| Q4: 7.3–8.5 mg/dL | 252 | 7.0 (6.2–7.9) | 1.34 (1.11–1.62) | 0.002 | 1.17 (0.96–1.43) | 0.12 |
| Q5: ≥8.6 mg/dL | 330 | 10.2 (9.1–11.4) | 1.96 (1.64–2.34) | <0.001 | 1.44 (1.17–1.77) | 0.001 |
| HF hospitalization |
| Q1: <5.4 mg/dL | 167 | 4.8 (4.2–5.6) | 1.00 (reference) | 1.00 (reference) |         |
| Q2: 5.4–6.2 mg/dL | 191 | 5.3 (4.6–6.1) | 1.10 (0.89–1.35) | 0.38 | 1.02 (0.83–1.26) | 0.84 |
| Q3: 6.3–7.2 mg/dL | 229 | 6.5 (5.7–7.4) | 1.34 (1.10–1.64) | 0.004 | 1.14 (0.93–1.40) | 0.21 |
| Q4: 7.3–8.5 mg/dL | 252 | 7.6 (6.7–8.6) | 1.56 (1.28–1.90) | <0.001 | 1.17 (0.95–1.44) | 0.14 |
| Q5: ≥8.6 mg/dL | 325 | 11.2 (10.1–12.5) | 2.28 (1.89–2.75) | <0.001 | 1.37 (1.11–1.70) | 0.004 |
| All-cause mortality |
| Q1: <5.4 mg/dL | 246 | 6.7 (5.9–7.6) | 1.00 (reference) | 1.00 (reference) |         |
| Q2: 5.4–6.2 mg/dL | 282 | 7.4 (6.6–8.4) | 1.10 (0.93–1.31) | 0.26 | 1.07 (0.89–1.27) | 0.48 |
| Q3: 6.3–7.2 mg/dL | 283 | 7.5 (6.7–8.4) | 1.11 (0.94–1.32) | 0.23 | 1.02 (0.85–1.21) | 0.86 |
| Q4: 7.3–8.5 mg/dL | 312 | 8.7 (7.7–9.7) | 1.29 (1.09–1.52) | 0.003 | 1.13 (0.95–1.35) | 0.18 |
| Q5: ≥8.6 mg/dL | 395 | 12.2 (11.1–13.5) | 1.82 (1.55–2.14) | <0.001 | 1.36 (1.13–1.64) | 0.001 |

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; PY, person years; Q, quintile.
*Adjusted for the following baseline-variables: age, sex, race, region, systolic blood pressure, heart rate, ejection fraction, New York Heart Association class, history of HF hospitalization, duration of HF, atrial fibrillation, diabetes, body mass index, prior myocardial infarction, prior stroke, estimated glomerular filtration rate, haemoglobin, sodium, albumin, randomized treatment (sacubitril/valsartan), diuretic dose, and log N-terminal pro-brain natriuretic peptide.
Serum uric acid and baseline characteristics

Patient characteristics according to quintile (Q1–Q5) of SUA are shown in Table 1. There were many differences between patients with higher and lower SUA. Patients with higher SUA were slightly younger and much more likely to be male. North American and Western European patients were over-represented among those with higher SUA, as were patients of Asian and Black race. Although some differences were small, the patients with higher SUA had an overall profile suggesting more advanced HF. Specifically, duration of HF was longer, NYHA class and KCCQ were worse and a history of prior HF hospitalization was more common. LVEF, systolic blood pressure and eGFR were lower and heart rate and NT-proBNP were higher. Of interest, most comorbidities were not substantially more common in patients with a higher SUA, except for atrial fibrillation (Q5 vs. Q1, 44.4% vs. 31.0%). Diuretic treatment was more frequent in patients with higher SUA (Q5 vs. Q1, 89.9% vs. 71.6%) and diuretic dose was also larger in those with higher SUA. Mineralocorticoid receptor antagonists were also used more often in patients with a higher SUA.

Serum uric acid and clinical outcomes

The rates of the clinical outcomes of interest according to baseline SUA quintile are shown in Table 2 and Figure 1. These are shown in relation to SUA displayed as a continuous variable in Figure 2. The primary composite outcome and both its components occurred more frequently in patients with higher UA concentrations although, after adjustment for other prognostic variables (including NT-proBNP, diuretic dose and eGFR) the increase in risk was only clearly seen in those with the highest levels (Q5, 8.6–17.1 mg/dL) using Q1 as reference. Spline analysis suggested a linear increase in risk above a serum concentration of around 7 mg/dL (Figure 2). Results were similar when including use of SUA lowering drugs at baseline in the multivariable model (supplementary material online, Table S1).

Effect of sacubitril/valsartan on outcomes according to serum uric acid level

The benefit of sacubitril/valsartan over enalapril was consistent across SUA quintiles for all outcomes of interest (Table 3; supplementary material online, Figure S3).

Effect of sacubitril/valsartan on serum uric acid level

During the run-in period, SUA decreased when switching from enalapril to sacubitril/valsartan and remained lower in the sacubitril/valsartan group than in the enalapril group at 4, 12, and 24 months after randomization (Figures 3–4 and Table 4). At 4 months after randomization, SUA was approximately 0.25 mg/dL (95% CI −0.33, −0.18) lower in the sacubitril/valsartan group and this difference persisted at 12 and 24 months.

Use of serum uric acid lowering agents before and after randomization

Very few patients (approximately 10%) were treated with a UA lowering agent at baseline and use did not vary according to SUA. UA lowering agents were initiated among 301 (7.3%) patients randomized to enalapril, as compared with 244 (6.0%) among those assigned to sacubitril/valsartan (between group P = 0.015).

Discussion

Although there are a number of reports of an association between high SUA and poor clinical outcomes in HF, it has not been clear whether UA is independently predictive when taking account of renal function and diuretic therapy, both of which increase UA and are themselves important markers of worse prognosis. More importantly, no prior report in patients with chronic HF included adjustment for natriuretic peptides, which are the single most powerful predictor of outcomes in HF. Our study addresses these gaps in the evidence to date. We found that even after accounting for these other variables, SUA remained a predictor of both death and HF hospitalization, although this was only apparent at concentrations above approximately 7 mg/dL and thus was most apparent in patients in the highest SUA quintile. Notably, we observed this relationship between SUA and outcomes in patients extensively treated with beta-blockers and mineralocorticoid receptor antagonists, in addition to full-dose renin–angiotensin system blockade (in most prior studies patients had not been treated with these contemporary therapies). PARADIGM-HF included patients with less severe HF than in prior reports on the role of SUA, and PARADIGM-HF was also a much more geographically representative cohort.

The precise nature of the link between SUA and prognosis in HF has been uncertain. One possibility is that high SUA is an epiphenomenon and just a marker of reduced excretion due to renal impairment or higher diuretic dose. However, our data suggest there may be additional potential mechanisms as SUA remained a predictor of outcome after correcting for those variables. High
Figure 2  Associations between serum uric acid level at randomization and outcomes. Adjusted for the following baseline variables: age, sex, race, region, systolic blood pressure, heart rate, ejection fraction, New York Heart Association class, history of heart failure (HF) hospitalization, duration of HF, atrial fibrillation, diabetes, body mass index, prior myocardial infarction, prior stroke, estimated glomerular filtration rate, haemoglobin, sodium, albumin, randomized treatment (sacubitril/valsartan), diuretic dose, and log N-terminal pro-brain natriuretic peptide. The reference is 7.0 mg/dL. CV, cardiovascular.

Table 3  Effects of sacubitril/valsartan vs. enalapril on outcomes according to uric acid quintile at randomization

|                                | Q1          | Q2          | Q3          | Q4          | Q5          | P-value for interaction |
|--------------------------------|-------------|-------------|-------------|-------------|-------------|-------------------------|
| Primary composite              | 0.75 (0.60–0.83) | 0.80 (0.65–0.99) | 0.73 (0.59–0.89) | 0.88 (0.73–1.07) | 0.81 (0.61–0.96) | 0.70 |
| CV death                       | 0.73 (0.55–0.98) | 0.82 (0.63–1.06) | 0.74 (0.57–0.97) | 0.91 (0.71–1.16) | 0.76 (0.61–0.95) | 0.72 |
| HF hospitalization             | 0.74 (0.54–1.00) | 0.80 (0.60–1.07) | 0.76 (0.59–0.99) | 0.82 (0.64–1.05) | 0.83 (0.67–1.03) | 0.98 |
| All-cause mortality            | 0.80 (0.62–1.03) | 0.83 (0.66–1.05) | 0.85 (0.67–1.07) | 0.93 (0.75–1.16) | 0.78 (0.64–0.95) | 0.80 |

CV, cardiovascular; HF, heart failure; Q, quintile.

SUA could also reflect increased xanthine oxidase activity and this, in turn, might result in oxidative stress which is thought to play a detrimental role in HF. It has also been suggested that UA itself has direct effects likely to be harmful in HF. For example, UA may have pro-inflammatory and proliferative actions and cause endothelial dysfunction. Likewise, UA may be damaging in the kidneys. While both possibilities are supported by experimental studies and mechanistic studies in humans, two small randomized clinical studies using xanthine oxidase inhibitors (which lowered SUA levels) have not shown clear clinical benefit in patients with HF.

In the Impact of Oxypurinol in Patients With Symptomatic Heart Failure (OPT-HF) study including 405 patients with HFrEF, oxypurinol reduced SUA by ∼2 mg/dL at 24 weeks without any clinical benefit overall, although post hoc analyses suggested possible benefits in patients with SUA > 9.5 mg/dL (approximating to Q5 in the present analysis). However, in the Effects of Xanthine...
Oxidase Inhibition in Hyperuricemic Heart Failure Patients (EXACT-HF) study, which included 253 patients with HFrEF and SUA ≥ 9.5 mg/dL, although allopurinol treatment reduced SUA by ∼4.2 mg/dL at 24 weeks, it did not improve clinical status, health-related quality of life or LVEF. Because of their limited size, neither of these studies definitively answers the question of whether lowering SUA improves clinical outcomes in HF.

In PARADIGM-HF, treatment with sacubitril/valsartan reduced SUA and did lead to better clinical outcomes. The reduction in SUA of approximately 0.25 mg/dL with sacubitril/valsartan was much smaller than in the studies mentioned above and the reduction was not of a magnitude one would expect to have a substantial effect on clinical outcomes. Whether (and by how much) this reduction in SUA contributed to the reduction in morbidity and mortality observed in PARADIGM-HF is unknown, given the many other beneficial mechanisms of action of sacubitril/valsartan. However, the possibility that lowering SUA might indeed be of value in HF cannot be excluded based on these findings.

The mechanism of the effect of sacubitril/valsartan on SUA is unknown. While losartan is known to have an uricosuric action, this is not the case for other ARBs, including valsartan. Inhibition of neprilysin may have such an effect as MDL 100,240, a dual neprilysin-ACE inhibitor, increased urinary UA excretion in a small (n = 12) study in human volunteers. We also found a significantly lower use of UA lowering agents after randomization in the sacubitril/valsartan compared with the enalapril group, which may be an additional clinical benefit of angiotensin receptor neprilysin inhibition.

SUA levels may also reflect oxidative stress and SUA itself may increase expression of cytokines and chemokines. Unfortunately, we did not evaluate these pathways in PARADIGM-HF to see whether the effect of sacubitril/valsartan on SUA was accompanied by changes in markers of inflammation.

The question remains as to whether SUA is a marker rather than a mediator of outcomes and our findings of an association between SUA and outcomes do not necessarily reflect cause and effect.

Our study has other limitations. Not all patients had SUA measured at every time point during follow-up. Patients with an eGFR < 30 mL/min/1.73 m² at screening, during the run-in period or at randomization were excluded, as were patients who experienced a decrease in eGFR > 25% (amended to > 35%) between screening and randomization. While measurement of SUA was pre-planned, not all of these analyses were. Finally, urinary UA was not measured.

In conclusion, SUA was an independent predictor of worse outcomes in PARADIGM-HF, even after multivariable adjustment. Compared with enalapril, sacubitril/valsartan reduced SUA and improved outcomes irrespective of SUA.

Figure 3 Effect of study drug on serum uric acid concentration. *P < 0.001 for sacubitril/valsartan vs. placebo in a repeated measures mixed model, with baseline score as a covariate, and treatment, region, time, and treatment by time interaction as fixed effects. During the first run-in all patients received enalapril but changed to sacubitril/valsartan during the second run-in, as illustrated below the curves.

Figure 4 Point prevalence of serum uric acid (SUA) according to randomized treatment. *P < 0.001. Grey bars illustrate number of patients with measurements at each time point.

© 2017 The Authors. European Journal of Heart Failure published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.
Table 4 Change in uric acid levels at different time points from randomization and from screening

|                          | Sacubitril/valsartan | Enalapril          |
|--------------------------|----------------------|--------------------|
|                          | n        | LSM (SE) | n | LSM (SE) | LSM of difference (95% CI) |
| Change from randomization (mg/dL) at |     |           |     |           |                           |
| 2 months                  | 2592 | 0.00 (0.025)  | 2574 | 0.23 (0.025)* | –0.23 (–0.16, 0.30)* |
| 4 months                  | 2846 | –0.01 (0.026) | 2838 | 0.25 (0.026)* | –0.26 (–0.33, 0.18)* |
| 12 months                 | 3529 | 0.01 (0.025)  | 3483 | 0.26 (0.025)* | –0.24 (–0.32, 0.17)* |
| 24 months                 | 2521 | 0.01 (0.032)  | 2428 | 0.29 (0.032)**| –0.28 (–0.37, 0.19)**|
| Change from screening (mg/dL) at |     |           |     |           |                           |
| 0 months (randomization)   | 4052 | –0.26 (0.021)* | 4076 | –0.30 (0.021)* | 0.04 (–0.01, 0.10) |
| 2 months after randomization | 2607 | –0.27 (0.027)** | 2593 | –0.05 (0.027)* | –0.21 (–0.29, 0.14)* |
| 4 months after randomization | 2869 | –0.26 (0.027)** | 2856 | –0.03 (0.027)  | –0.23 (–0.31, 0.16) |
| 12 months after randomization | 3572 | –0.25 (0.026)** | 3521 | –0.02 (0.026)  | –0.23 (–0.30, 0.15) |
| 24 months after randomization | 2558 | –0.25 (0.032)** | 2464 | 0.01 (0.033)  | –0.26 (–0.35, 0.17)** |

Data are least square means (LSM) with standard errors (SE) based on a repeated measures mixed model—with the baseline score as a covariate, and treatment, time, and treatment by time interaction as fixed effects. CI, confidence interval.

*P < 0.05, **P < 0.0001.

## Supplementary Information

### Additional Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** PARADIGM-HF Investigators.

**Figure S1.** Distribution of serum uric acid concentrations at randomization according to sex and region.

**Figure S2.** Distribution of serum uric acid concentrations at randomization according to sex and region.

**Figure S3.** Hazard ratio of sacubitril/valsartan compared with enalapril for the risk of the primary endpoint according to uric acid level at randomization (green line).

**Table S1.** Risk of various endpoints according to uric acid levels (SUA) at randomization in a model including use of SUA lowering drugs.

### Funding

PARADIGM-HF was funded by Novartis. U.M.M. was supported by a research grant from the Danish Heart Foundation (grant number 16-R107-A6786–22960).

### Conflict of interest

With the exception of U.M.M. and S.L.K., all authors or their institutions have received payments from Novartis for their involvement in PARADIGM-HF or other trials/activities funded by Novartis. M.P.L., M.F.P. and V.C.S. are employees of Novartis. U.M.M. has received honoraria for lectures from MSD and Novo Nordisk outside the submitted work.

### References

1. Bergamini C, Cicoria M, Rossi A, Vassanelli C. Oxidative stress and hyperuricaemia: pathophysiology, clinical relevance, and therapeutic implications in chronic heart failure. *Eur J Heart Fail* 2009;11:444–452.
2. Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. *Semin Nephrol* 2005;25:39–42.
3. Feg DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med* 2008;359:1811–1821.
4. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knossalla C, Davos CH, Cicoria M, Shamim W, Kemp M, Segal R, Osterziel KJ, Lamy F, Heitzer R, Ponikowski P, Coats AJ. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. *Circulation* 2003;107:1991–1997.
5. Hare JM, Johnson RJ. Uric acid predicts clinical outcomes in heart failure: insights regarding the role of xanthine oxidase and uric acid in disease pathophysiology. *Circulation* 2003;107:1951–1953.
6. Vaduganathan M, Greene S, Ambrosy AP, Mentz RJ, Subacius HP, Chioncel O, Maggioni AP, Swedberg K, Zannad F, Konstam MA, Senni M, Givertz MM, Butler J, Gheorghiade M. EVEREST Trial Investigators. Relation of serum uric acid levels and outcomes among patients hospitalized for worsening heart failure with reduced ejection fraction (from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan Trial). *Am J Cardiol* 2014;114:1713–1721.
7. Hare JM, Mangal B, Brown J, Fisher C, Jr., Freudenberg R, Colucci WS, Mann DL, Liu P, Givertz MM, Schwartz RP. OPT-CHF Investigators. Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. *J Am Coll Cardiol* 2008;51:2301–2309.
8. Givertz MM, Anstrom KJ, Redfield MM, Deswal A, Haddad H, Butler J, Tang WH, Dunlap ME, LeWinter MM, Mann DL, Felker GM, O’Connor CM, Goldsmith SR, Offili EO, Salsberg MT, Margules KB, Cappola TP, Konstam MA, Semigran MJ, McNulty SE, Lee KL, Shah MR, Hernandez AF, NHLBI Heart Failure Clinical Research Network. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients: the Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) Study. *Circulation* 2015;131:1763–1771.
9. McMurray JJ, Packer M, Solomon SD. Nephritis inhibition in heart failure. *N Engl J Med* 2014;371:2326–2337.
10. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rolleau J, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Committee and Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail* 2013;15:1062–1073.
11. Packer M, McMurray JJ, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rolleau JL, Shi VC, Solomon SD, Swedberg K, Zile M, Andersen K, Arango JL, Arnold JH, Belohlavek J, Bohm M, Boysov S, Burgess LJ, Cabrera W, Calvo C, Chen CH, Dukat A, Duarte YC, Egelis A, Fu M, Gomez E, Gonzalez-Medina A, Hagege AA, Huang J, Katsova T, Ktnschrooakun S, Kim KS, Kozan O, Llamas EB, Martinez F, Merkely B, Mendoza I, Mostard A, Negruz-Sawakeaa M, Pehukurinen K, Ramires FJ, Refsgaard J, Senni M, Sibulo AS Jr, Silva-Cardoso K, Squire IB, Starling RC, Tearlink JR, Vanheace J, Vinereanu D, Wong RC; PARADIGM-HF Investigators and Coordinators. Angiotensin receptor neprilysin inhibition as an alternative to combined ACEI/ARB therapy in chronic heart failure: the PARADIGM-HF trial. *Eur J Heart Fail* 2013;15:1062–1073.
12. Kanbay M, Segal M, Afsar B, Kang DH, Rodriguez-Iturbe B, Johnson RJ. The role of uric acid in the pathogenesis of human cardiovascular disease. *Heart* 2013;99:759–766.

13. Kang DH. A role for uric acid in the progression of renal disease. *J Am Soc Nephrol* 2002;13:2888–2897.

14. Wolff ML, Cruz JL, Vanderman AJ, Brown JN. The effect of angiotensin II receptor blockers on hyperuricemia. *Ther Adv Chronic Dis* 2015;6:339–346.

15. Iwanaga T, Sato M, Maeda T, Oghara T, Tamai I. Concentration-dependent mode of interaction of angiotensin II receptor blockers with uric acid transporter. *J Pharmacal Exp Ther* 2007;320:211–217.

16. Rousso P, Buclin T, Nussberger J, Decosterd LA, La Roche SD, Brunner-Ferber F, Brunner HR, Biollaz J. Effects of a dual inhibitor of angiotensin converting enzyme and neutral endopeptidase, MDL 100,240, on endocrine and renal functions in healthy volunteers. *J Hypertens* 1999;17:427–437.

17. Keenan T, Zhao W, Rasheed A, Ho WK, Malik R, Felix JF, Young R, Shah N, Samuel M, Sheikh N, Mucksavage ML, Shah O, Li J, Morley M, Laster A, Mallick NH, Zaman KS, Ishaq M, Rasheed SZ, Memon FU, Ahmed F, Hanif B, Lakhani MS, Fahim M, Ishaq M, Sharhfa NK, Ahmed N, Mahmoud K, Iqbal W, Akhtar S, Raheel R, O’Donnell CJ, Hengstenberg C, Marz W, Kshiresan S, Samani N, Goel A, Hopewell JC, Chambers J, Cheng YC, Sharma P, Yang Q, Rosand J, Boncoraglio GB, Kazmi SU, Hakonarson H, Kottgen A, Kalogepoulos A, Fressard P, Kamal A, Dichgans M, Cappola T, Reilly MP, Danesh J, Rader DJ, Voight BF, Saleheen D. Causal assessment of serum urate levels in cardiometabolic diseases through a Mendelian randomization study. *J Am Coll Cardiol* 2016;67:407–416.