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**RESEARCH ARTICLE**

# Cardiovascular risk associated with serum potassium in the context of mineralocorticoid receptor antagonist use in patients with heart failure and left ventricular dysfunction

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**Background** To assess the prognostic value of mineralocorticoid receptor antagonist (MRA) initiation and change in serum potassium ($K^+$) during follow-up in patients post-acute myocardial infarction with left ventricular dysfunction or chronic heart failure (HF) and reduced ejection fraction (HFrEF).

**Methods and results** Risk scores for predicting cardiovascular death (primary outcome), hospitalization for HF and all-cause death were developed. $K^+$ and other relevant time-updated clinical and biological variables were added to conventional prognostic factors when constructing these new models. EPHESUS ($n = 6632$) was the derivation cohort, while EMPHASIS-HF (chronic HF, $n = 2737$) was used as external validation cohort. The final cardiovascular death risk score included medical history, clinical and biological parameters (e.g. $K^+$, below or above the normal range of 4–5 mmol/L, estimated glomerular filtration rate, and anaemia), as well as aspects of treatment (any diuretic usage, MRA use or discontinuation, and beta-blocker use). The risk score performed well in both the derivation and validation cohorts and outperformed the MAGGIC score. A web-based calculator was created to allow easy determination of the risk score (http://cic-p-nancy.fr/CardiovascularriskscoreCalculator/).

**Conclusion** Adding time-updated variables, including $K^+$ and MRA treatment, improved risk prediction of cardiovascular death (on top of the MAGGIC score) in patients with HF eligible for renin–angiotensin system inhibitors and MRA therapy. This new risk score including MRA usage and $K^+$ may be of value in helping physicians to better use MRAs, avoid unnecessary and potentially detrimental permanent discontinuations, and therefore improving cardiovascular outcomes in patients with chronic HFrEF or HF after acute myocardial infarction with left ventricular dysfunction.

**Keywords** Hyperkalaemia • Hypokalaemia • Heart failure with reduced ejection fraction • Mineralocorticoid receptor antagonist • Risk score

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# Introduction

Hypokalaemia and hyperkalaemia have been consistently shown to be associated with increased morbidity and mortality in various populations [e.g. hypertension,[1] acute[2,3] and chronic heart failure[4,5] (HF), acute myocardial infarction (AMI),[6,7] chronic kidney disease, and the general population].[8] There are few validated predictors of the risk of cardiovascular (CV) death associated with serum potassium ($K^+$) abnormalities in HF patients receiving renin–angiotensin–aldosterone system (RAAS) blockers. Therefore, we have developed a score describing the risk of CV events associated with serum $K^+$ in patients receiving mineralocorticoid receptor antagonist (MRA) therapy. This score could help clinicians in decision-making regarding the safe and effective use of MRAs in patients with HF and reduced ejection fraction (HFrEF) and in those with left ventricular dysfunction and HF after AMI.

We took advantage of data collected in major clinical trials with frequent serum $K^+$ monitoring and adjudicated CV death and other relevant CV outcomes.

# Methods

## Patient populations

The design and main results of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial have previously been reported.[9] The EPHESUS study enrolled 6632 patients with HF after AMI complicated by left ventricular systolic dysfunction (ejection fraction <40%). Patients were entered into the study from 3 to 14 days after AMI. All patients were randomly assigned to treatment with eplerenone 25 mg/day or placebo.

The design, patient eligibility criteria, study procedure and main results of the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial have also been previously reported.[10] In this randomized double-blind trial, 2737 patients with New York Heart Association (NYHA) class II HF and an ejection fraction ≤35% were randomly assigned to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy.

## Statistical analysis

All analyses were performed using the R software (the R Foundation for Statistical Computing, Vienna, Austria). Baseline characteristics of these two populations were described using mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables.

Candidate variables are listed in online supplementary *Methods S1*.[11,12] Cox proportional hazards models with time-updated covariates and interactive backward variable selection were used to build risk scores for the three following endpoints: (i) CV death, (ii) hospitalization for HF, and (iii) all-cause death. A $P < 0.05$ was used to remove non-significant variables from the Cox model. Hazard ratios (HR) are presented with their 95% confidence intervals. A points-based risk scoring system was derived from each final Cox model according to the following principle: points were attributed by multiplying the regression coefficients by 10, then by rounding the values to the nearest integer, and risk score was finally calculated as the sum of points attributed to each variable.

The predicted risk at 1 year was plotted as a function of the risk score (more details on predicted risk calculation in online supplementary *Methods S1*). Risk score discrimination was assessed using the Harrell's c-index.[13] As described in Ketchum *et al.*,[14] predicted risk at 1 year and 2 years by deciles of risk score was plotted against the observed risk estimated by the Kaplan–Meier method from which a correlation coefficient was calculated. The calibration of the model was assessed using the Hosmer–Lemeshow goodness of fit test.[15]

As a supplementary analysis, we evaluated the effect <30 days and ≥30 days after measurement for each clinical/biological time-updated variable and reported corresponding *P*-value for interaction.

# Results

The baseline characteristics of patients in EPHESUS and EMPHASIS-HF are presented in *Table 1*. The median [interquartile range (IQR)] follow-up was 16 (12–20) months in EPHESUS and 21 (10–33) in EMPHASIS-HF. The anticipated number of serum $K^+$ measurements according to the protocol was 10 (8–11) and 7 (5–10) in each trial, respectively. The median (IQR) number of actual serum $K^+$ measurements was 11 (9–13) and 8 (5–11), respectively, i.e. some additional measurements were performed after a clinical event or after a non-anticipated medication change. The median (IQR) number of serum $K^+$ measurements per year per patient was 8.2 (7.0–10.2) and 4.5 (3.9–6.1), respectively.

*Table 2* shows the predictive models for CV death and hospitalization for HF and how the risk score is derived (online supplementary *Table S1* also presents the model for all-cause death). The CV death score included certain aspects of medical history, clinical variables (age, systolic blood pressure, heart rate, body mass index, NYHA class) and biological parameters [e.g. serum $K^+$, below or above a normal range of 4–5 mmol/L, estimated glomerular filtration rate (eGFR), anaemia] and certain treatments (diuretic use, MRA current use or discontinuation, beta-blocker use). *Figure 1* presents the 1-year predicted risk of CV death and hospitalization for HF, according to score, while online supplementary *Figure S1* presents the 1-year predicted risk of all-cause death.

## Discrimination and calibration of the model in derivation and validation cohorts

The model performed well in both the derivation and validation cohorts. The C-indexes for the CV risk and HF hospitalization scores in EPHESUS ranged from 0.78 to 0.79 and were approximately 0.75 for each endpoint in EMPHASIS-HF (*Table 2*). *Figure 2* presents the predicted compared with observed risks (CV death, hospitalization for HF), by deciles of risk score, in the derivation and validation cohorts at 1 and 2 years. The correlation coefficients between predicted and observed survival were very high (close to 0.99) in both derivation and validation cohorts. The Hosmer–Lemeshow goodness of fit statistic confirmed model accuracy in the EPHESUS derivation ($P = 0.99$ for CV death and 0.91 for HF hospitalization) at 1 year. In the EMPHASIS-HF cohort, a slight overestimation of predicted risk of CV death was observed at 1 year ($P = 0.057$), which was not the case for

**Table 1 Baseline characteristics and outcomes of EPHESUS and EMPHASIS-HF patients**

| | EPHESUS ($n = 6632$) | | EMPHASIS-HF ($n = 2737$) | |
|---|---|---|---|---|
| **Characteristics** | ***n*** | **Mean ± SD/*n* (%)** | ***n*** | **Mean ± SD/*n* (%)** |
| Age (years) | 6632 | 64 ± 12 | 2737 | 69 ± 8 |
| Gender | 6632 | | 2737 | |
| Male | | 4714 (71.1) | | 2127 (77.7) |
| Female | | 1918 (28.9) | | 610 (22.3) |
| Cigarette smoking status | 6627 | | 2737 | |
| Never smoker | | 2587 (39.0) | | 1223 (44.7) |
| Current smoker | | 2043 (30.8) | | 293 (10.7) |
| Former smoker | | 1997 (30.1) | | 1221 (44.6) |
| History of alcohol abuse | 6615 | 83 (1.3) | 2737 | 16 (0.6) |
| Body mass index (kg/m$^2$) | 6611 | 27.4 ± 4.5 | 2724 | 27.5 ± 4.9 |
| Systolic BP (mmHg) | 6630 | 119 ± 16 | 2736 | 124 ± 17 |
| Diastolic BP (mmHg) | 6630 | 72 ± 11 | 2736 | 75 ± 10 |
| Heart rate (bpm) | 6628 | 75 ± 12 | 2735 | 72 ± 12 |
| Potassium (mmol/L) | 6586 | 4.3 ± 0.4 | 2731 | 4.3 ± 0.4 |
| eGFR (mL/min/1.73 m$^2$) | 6587 | 68 ± 21 | 2725 | 65 ± 18 |
| Haemoglobin (g/dL) | 6556 | 13.3 ± 1.7 | 2669 | 13.8 ± 1.6 |
| Anaemia | 6556 | 2160 (32.9) | 2669 | 616 (23.1) |
| Medical history | | | | |
| Previous MI | 6632 | 1802 (27.2) | 2734 | 1380 (50.5) |
| Atrial fibrillation | 6632 | 874 (13.2) | 2737 | 844 (30.8) |
| Renal insufficiency | 6632 | 434 (6.5) | 2737 | 214 (7.8) |
| COPD | 6632 | 625 (9.4) | 2734 | 391 (14.3) |
| Previous hospitalization for HF[a] | 6632 | 975 (14.7) | 2734 | 1438 (52.6) |
| Hypertension | 6632 | 4007 (60.4) | 2737 | 1819 (66.5) |
| Diabetes | 6632 | 2142 (32.3) | 2737 | 859 (31.4) |
| Peripheral vascular disease | 6632 | 823 (12.4) | 2737 | 94 (3.4) |
| Medication | | | | |
| Any diuretic use | 6632 | 3984 (60.1) | 2721 | 2326 (85.5) |
| Beta-blocker use | 6632 | 4961 (74.8) | 2721 | 2374 (87.2) |
| ACEi use | 6632 | 5616 (84.7) | 2721 | 2124 (78.1) |
| ARB use | 6632 | 216 (3.3) | 2721 | 527 (19.4) |
| ACEi/ARB use | 6632 | 5751 (86.7) | 2721 | 2558 (94.0) |
| Study treatment | 6632 | | 2737 | |
| Placebo | | 3313 (50.0) | | 1373 (50.2) |
| Eplerenone | | 3319 (50.0) | | 1364 (49.8) |
| Study treatment taken or not at baseline | 6632 | | 2737 | |
| Not taken | | 24 (0.4) | | 7 (0.3) |
| Taken | | 6608 (99.6) | | 2730 (99.7) |
| Outcomes | | | | |
| All-cause death | 6632 | 1032 (15.6) | 2737 | 384 (14.0) |
| CV death | 6632 | 890 (13.4) | 2737 | 332 (12.1) |
| Hospitalization for HF | 6632 | 855 (12.9) | 2737 | 417 (15.2) |
| CV death/hospitalization for HF | 6632 | 1451 (21.9) | 2737 | 605 (22.1) |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP blood pressure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MI myocardial infarction; SD, standard deviation.
[a]Defined as previous episodes of HF in the EPHESUS cohort.

hospitalization for HF ($P = 0.25$). At 2 years, the two risk scores were well calibrated in the two cohorts (all $P > 0.30$).

The risk scores significantly outperformed the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC)[16] score for predicting outcomes in both EPHESUS (C-index difference of 0.044 for CV death and 0.063 for hospitalization for HF) and EMPHASIS-HF (C-index difference of 0.055 for CV death and 0.064 for hospitalization for HF) (online supplementary *Table S2*). The distribution of risk score categories across the two trials is presented in online supplementary *Table S3*.

A web-based application was created to allow an easy determination of the complete risk score as a

**Table 2 Risk scores of cardiovascular death and hospitalization for heart failure developed in the EPHESUS cohort and validated in the EMPHASIS-HF cohort**

| | CV death | | | | Hospitalization for HF | | | |
|---|---|---|---|---|---|---|---|---|
| **Variables** | **HR (95% CI)** | ***P*-value** | **$\beta$** | **Points** | **HR (95% CI)** | ***P*-value** | **$\beta$** | **Points** |
| **Time-updated variables** | | | | | | | | |
| Potassium (mmol/L) | | | | | | | | |
| <3.5 | 2.09 (1.49–2.92) | <0.0001 | 0.74 | 7 | 2.17 (1.48–3.19) | <0.0001 | 0.78 | 8 |
| 3.5–3.9 | 1.30 (1.05–1.61) | 0.017 | 0.26 | 3 | 1.50 (1.22–1.85) | 0.0001 | 0.41 | 4 |
| 4–5 | 1.00 | – | – | 0 | 1.00 | – | – | 0 |
| 5.1–5.5 | 1.30 (1.04–1.62) | 0.019 | 0.26 | 3 | 1.00 (0.79–1.27) | 0.99 | 0.00 | 0 |
| >5.5 | 2.10 (1.41–3.13) | 0.0003 | 0.74 | 7 | 2.22 (1.51–3.26) | <0.0001 | 0.80 | 8 |
| eGFR (mL/min/1.73 $m^2$) | | | | | | | | |
| <30 | 2.53 (1.76–3.62) | <0.0001 | 0.93 | 9 | 2.24 (1.57–3.19) | <0.0001 | 0.81 | 8 |
| 30–44 | 1.70 (1.24–2.34) | 0.001 | 0.53 | 5 | 2.10 (1.58–2.79) | <0.0001 | 0.74 | 7 |
| 45–59 | 1.31 (0.96–1.77) | 0.084 | 0.27 | 3 | 1.51 (1.15–1.99) | 0.003 | 0.41 | 4 |
| 60–89 | 1.16 (0.87–1.53) | 0.31 | 0.15 | 1 | 1.09 (0.83–1.41) | 0.54 | 0.08 | 1 |
| ≥90 | 1.00 | – | – | 0 | 1.00 | – | – | 0 |
| Anaemia | 1.20 (1.03–1.39) | 0.020 | 0.18 | 2 | 1.77 (1.52–2.05) | <0.0001 | 0.57 | 6 |
| Body mass index (kg/$m^2$) | | | | | | | | |
| <18.5 | 1.69 (1.01–2.81) | 0.044 | 0.52 | 5 | – | – | – | – |
| 18.5–24.9 | 1.34 (1.14–1.57) | 0.0004 | 0.29 | 3 | – | – | – | – |
| 25–29.9 | 1.00 | – | – | 0 | – | – | – | – |
| ≥30 | 1.04 (0.86–1.27) | 0.66 | 0.04 | 0 | – | – | – | – |
| Systolic BP (mmHg) | | | | | | | | |
| <100 | 3.13 (2.44–4.00) | <0.0001 | 1.14 | 11 | 1.99 (1.50–2.64) | <0.0001 | 0.69 | 7 |
| 100–119 | 1.51 (1.23–1.85) | <0.0001 | 0.41 | 4 | 1.52 (1.25–1.85) | <0.0001 | 0.42 | 4 |
| 120–139 | 1.17 (0.95–1.43) | 0.13 | 0.16 | 2 | 1.05 (0.87–1.28) | 0.61 | 0.05 | 1 |
| ≥140 | 1.00 | – | – | 0 | 1.00 | – | – | 0 |
| Heart rate (bpm) | | | | | | | | |
| ≤60 | 1.00 | – | – | 0 | 1.00 | – | – | 0 |
| 61–80 | 1.08 (0.88–1.34) | 0.46 | 0.08 | 1 | 1.35 (1.07–1.69) | 0.010 | 0.30 | 3 |
| 81–100 | 1.75 (1.38–2.22) | <0.0001 | 0.56 | 6 | 2.35 (1.83–3.01) | <0.0001 | 0.85 | 9 |
| >100 | 3.21 (2.23–4.61) | <0.0001 | 1.17 | 12 | 4.04 (2.63–6.20) | <0.0001 | 1.40 | 14 |
| NYHA class | | | | | | | | |
| I | 1.00 | – | – | 0 | 1.00 | – | – | 0 |
| II | 1.23 (1.00–1.51) | 0.048 | 0.21 | 2 | 1.28 (1.05–1.56) | 0.013 | 0.25 | 2 |
| III/IV | 3.22 (2.60–4.00) | <0.0001 | 1.17 | 12 | 2.88 (2.33–3.55) | <0.0001 | 1.06 | 11 |
| Age (years) | | | | | | | | |
| <65 | 1.00 | – | – | 0 | – | – | – | – |
| 65–74 | 1.29 (1.07–1.56) | 0.009 | 0.26 | 3 | – | – | – | – |
| ≥75 | 1.39 (1.12–1.71) | 0.002 | 0.33 | 3 | – | – | – | – |
| Permanent discontinuation of study treatment | 1.66 (1.38–2.00) | <0.0001 | 0.51 | 5 | – | – | – | – |
| **Fixed variables (baseline)** | | | | | | | | |
| Previous MI | 1.24 (1.06–1.46) | 0.007 | 0.22 | 2 | 1.38 (1.18–1.61) | <0.0001 | 0.32 | 3 |
| Atrial fibrillation | 1.26 (1.06–1.49) | 0.010 | 0.23 | 2 | 1.23 (1.03–1.46) | 0.024 | 0.20 | 2 |
| Previous hospitalization for HF | 1.26 (1.06–1.51) | 0.010 | 0.23 | 2 | 1.26 (1.05–1.50) | 0.011 | 0.23 | 2 |
| Hypertension | – | – | – | – | 1.31 (1.11–1.54) | 0.001 | 0.27 | 3 |
| Diabetes | 1.21 (1.04–1.41) | 0.012 | 0.19 | 2 | 1.26 (1.08–1.46) | 0.003 | 0.23 | 2 |
| Peripheral vascular disease | 1.34 (1.12–1.60) | 0.002 | 0.29 | 3 | 1.37 (1.14–1.64) | 0.0006 | 0.32 | 3 |
| Any diuretic use | 1.30 (1.09–1.55) | 0.003 | 0.26 | 3 | 1.67 (1.39–2.00) | <0.0001 | 0.51 | 5 |
| No beta-blocker use | 1.34 (1.16–1.56) | <0.0001 | 0.30 | 3 | – | – | – | – |
| Study treatment | | | | | | | | |
| Eplerenone | 0.84 (0.73–0.97) | 0.017 | −0.17 | 0 | 0.81 (0.70–0.93) | 0.004 | −0.21 | 0 |
| Placebo/not on eplerenone | 1.00 | – | – | 2 | 1.00 | – | – | 2 |
| C-index (95% CI) | | | | | | | | |
| Derivation (EPHESUS) | 0.783 (0.766–0.800) | | | | 0.781 (0.765–0.797) | | | |
| Validation (EMPHASIS-HF) | 0.747 (0.718–0.777) | | | | 0.743 (0.716–0.769) | | | |

BP, blood pressure; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

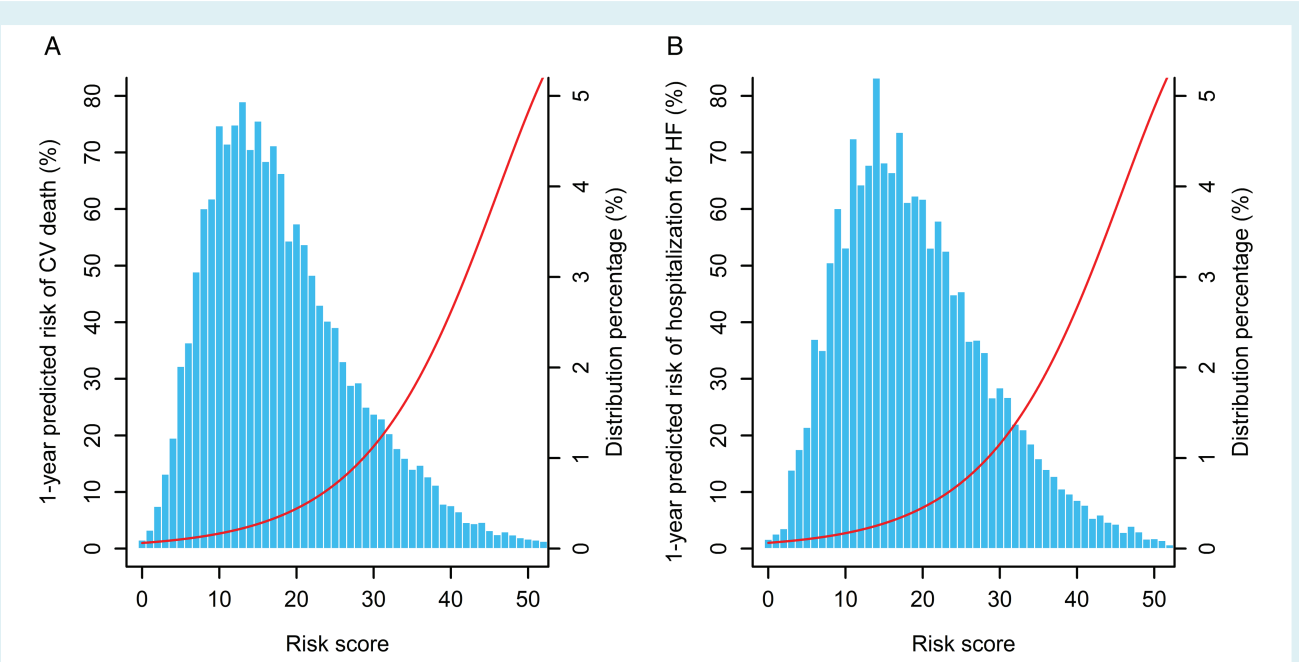


**Figure 1** One-year predicted risk of cardiovascular (CV) death and hospitalization for heart failure (HF) as a function of risk score.

function of available parameters to the physician after 6 months, 1 year and 2 years. The calculator is available at http://cic-p-nancy.fr/CardiovascularriskscoreCalculator/.

## Interaction between the number of potassium measurements and the value of the prognostic score

We assessed the interaction between the prognostic score for each outcome and the number of $K^+$ measurements made during follow-up (using tertiles of $K^+$ measurements; online supplementary *Table S4*). We identified a significant interaction for all the outcomes examined in EMPHASIS-HF and EPHESUS (all $P < 0.05$ for CV mortality, HF hospitalization and all-cause mortality). Overall, the association between the risk score (per 10 point increase) and outcome increased with an increasing number of $K^+$ measurements. In EPHESUS, the HR for CV death ranged from 2.05 (1.91–2.19) in the first tertile of $K^+$ measurements to 3.77 (3.18–4.46) and 3.86 (3.34–4.46) in the second and third tertiles. In EMPHASIS-HF the HR for CV death increased from 1.92 (1.63–2.25) in the first tertile to 2.96 (2.27–3.87) in the third tertile.

## Sensitivity analyses

We identified significant interactions between systolic blood pressure, heart rate, NYHA class with the time after measurement (<30 days or ≥30 days) for CV death; this was not seen for other variables (online supplementary *Table S5*). The association between $K^+$ and CV death was as follows: <30 days, HR 2.57 (1.64–4.04) for $K^+ > 5.5$ mmol/L; ≥30 days, HR 1.26 (0.56–2.89) for $K^+ > 5.5$ mmol/L (4–5 mmol/L as reference in each period).

In contrast, we identified a significant interaction between $K^+$ and time after measurement for worsening HF hospitalization. Both hypo- and hyperkalaemia were strongly and significantly associated with this outcome <30 days but not for the ≥30 day period (<30 days: HR 2.62 (1.74–3.94) for $K^+ < 3.5$ mmol/L, 2.63 (1.73–4.01) for $K^+ > 5.5$ mmol/L; ≥30 days: HR 0.86 (0.27–2.71) for $K^+ < 3.5$ mmol/L, 1.39 (0.56–3.45) for $K^+ > 5.5$ mmol/L) (online supplementary *Table S6*).

In an additional analysis, we assessed the association of time-updated serum $K^+$ and eGFR with outcomes further adjusting for dose of MRA and loop diuretics during follow-up in the EPHESUS trial. The association between hyper- and hypokalaemia, as well as eGFR, and outcomes remained unchanged (online supplementary *Table S7*).

# Discussion

To our knowledge this is the first attempt to integrate serial $K^+$ measurements in the context of initiation and maintenance of MRA treatment in a risk model. The model was created using data from a cohort of patients with AMI complicated by a reduced left ventricular ejection fraction and HF and validated in a second, chronic HF, population. A computerized score has been derived from the risk model and made available as an online tool for convenience of use. Furthermore, a sensitivity analysis identified that highest or lowest values of $K^+$ carried a particularly high risk for events occurring within 30 days, which strengthens the clinical relevance of our findings.

Importantly, we hope that this tool will enable a better use of MRAs by the medical community, avoiding unnecessary permanent discontinuations. Our risk score has several advantages compared

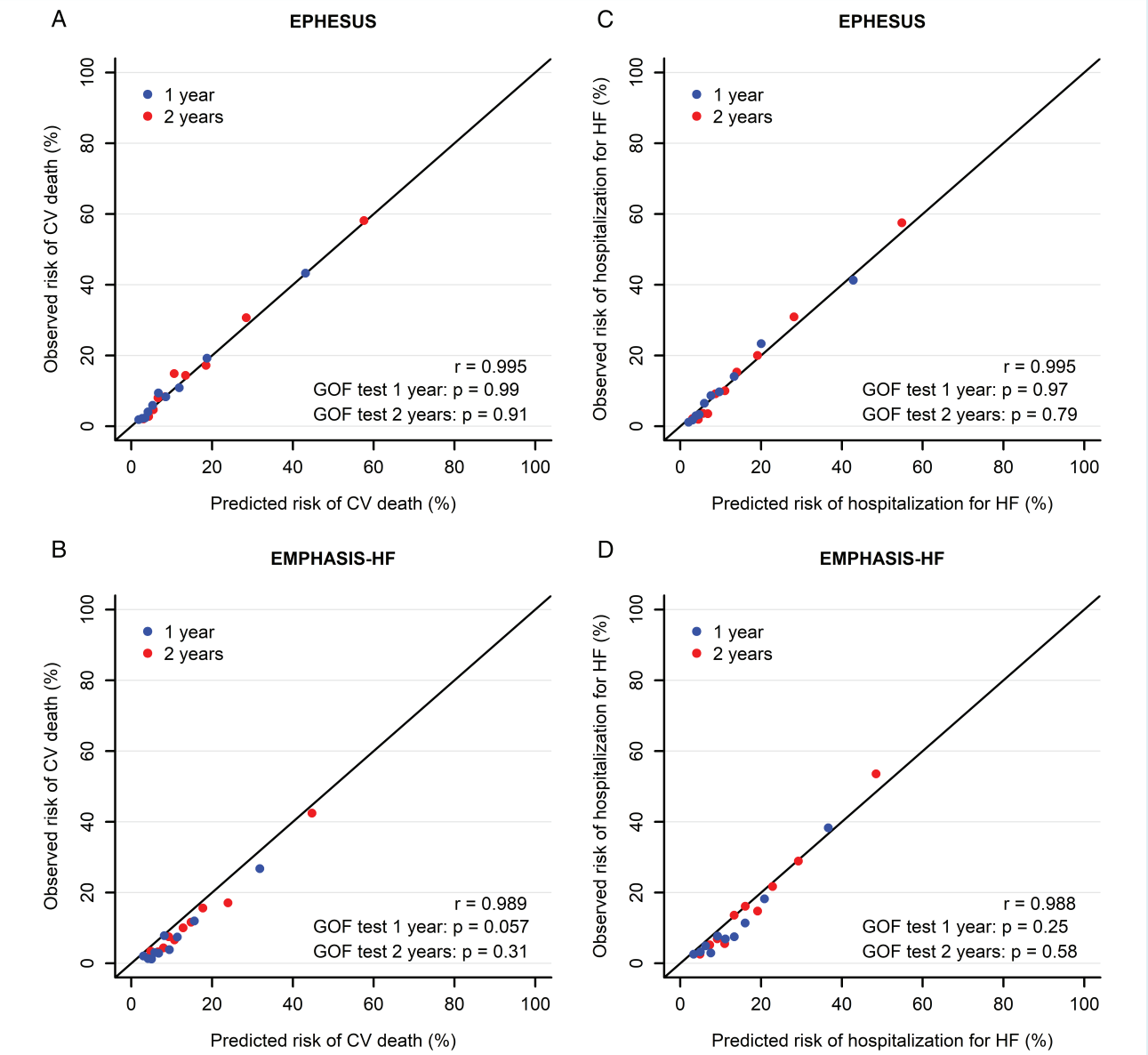


**Figure 2** Predicted vs. observed risk by deciles of risk score in the EPHESUS derivation cohort (*A*, *C*) and EMPHASIS-HF (*B*, *D*) validation cohort. CV, cardiovascular; GOF, goodness of fit; HF, heart failure.

to previous ones. It is time-updated in contrast with all/most of the previously published risk scores for HF.[14,17–19] This methodological feature permitted us to precisely evaluate the association between repeated $K^+$ concentrations and CV outcomes. This association could not be evaluated with previous risk scores as hyper- and hypokalaemia were usually exclusion criteria in clinical trials. Including time-updated variables in risk estimation is clinically feasible since patients are repeatedly reviewed in routine practice, and serial serum $K^+$ monitoring is strongly advised in HF guidelines. Our approach is also relevant, since initiation and discontinuation of HF therapies such as MRAs during the patient clinical course are additional risk modifiers which should be accounted for.

As a result, the initiation and subsequent adjustment of MRA is included in our score and the potential negative effect of stopping this treatment is also estimated. In the Seattle Heart Failure Model (SHFM) score,[17] the benefits of using a MRA were indirectly estimated from large published randomized trials and meta-analyses. In the Seattle Post Myocardial Infarction Model (SPIM) score,[14] the effect of MRA use on CV outcomes was not directly evaluable as it was a component of a variable entitled 'number of cardiac evidence-based medicines' (ranging from 0 to 5), with four other HF treatments including aspirin, beta-blocker, statin, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs). Moreover, medications are accounted for in SPIM only at a single time point.

Adding time-updated variables, including $K^+$ and MRA treatment, improved risk prediction of CV death (on top of the MAGGIC score[16]) in patients with HF eligible for renin–angiotensin system inhibitors and MRA therapy. We however acknowledge the value of others comparing scores on their more modern-day databases in the future.

The present risk score was developed using data from a cohort of patients with AMI complicated by a reduced left ventricular ejection fraction and HF and validated in a second, chronic HF, population. This emphasizes its wide applicability to patients with HFrEF regardless of the setting (i.e. *de novo* ischaemic HF, chronic HF). This validation process contrasts with other scores developed previously in HF patients.

Independent of history, clinical and laboratory parameters, and treatment parameters (diuretics, beta-blockers, MRA initiation and maintenance), patients with an abnormal $K^+$ displayed poorer outcomes. These results corroborate and strengthen previous results. In a retrospective cohort study using the Cerner Health Facts database, which included 38 689 patients with biomarker-confirmed AMI admitted to 67 US hospitals between 1 January 2000 and 31 December 2008, Goyal *et al.*[6] reported a U-shaped relationship between mean post-admission serum $K^+$ level and in-hospital mortality that persisted after multivariable adjustment. A large proportion (19.2% to 47.8%) of the AMI patient population reported in this registry had a history of HF. Unfortunately, Goya *et al.* did not report on MRA use in their patient population and therefore their results were not adjusted for MRA use.

Our results further show the benefit of initial and sustained MRA intake over time in the post-AMI population, irrespective of serum $K^+$ concentrations measured anytime during follow-up, since patients not assigned MRA or who discontinued MRA displayed a poorer prognosis, with no significant interaction (data not shown). Furthermore, the prognostic value of serum $K^+$ anytime below or higher than the normal range of 4–5 mmol/L in this post-AMI and left ventricular systolic dysfunction setting was observed independent of the prognostic value of eGFR with no significant interaction (data not shown).

In the chronic HF setting, we previously reported in the EMPHASIS-HF cohort that incident hypokalaemia below $K^+$ of 4 mmol/L during follow-up was common (42.6%), suggesting that physicians may not be fully aware of the risk associated with mild hypokalaemia and therefore not take action to maintain normal $K^+$. Indeed, patients with hypokalaemia during follow-up were at increased risk of CV death and/or HF hospitalization. They had a better prognosis when treated with the MRA eplerenone compared with placebo.[20] In the subset of patients with baseline hypokalaemia, a significantly greater percentage of patients in the eplerenone group exhibited a serum K+ $\geq$4.0 mmol/L at 1 month than in the placebo group. A mediation analysis showed that the increase in $K^+$ >4.0 mmol/L at 1 month after randomization accounted for 26.0% (0.6–51.4%) of the effect of eplerenone treatment ($P = 0.04$).[20] Conversely, episodes of hyperkalaemia or worsening renal function were common in these patients receiving optimal therapy, including ACEi/ARBs and beta-blockers. The addition of the MRA eplerenone increased the rate of worsening renal function and hyperkalaemia. However, these adverse outcomes did not negate the major survival benefit of eplerenone when electrolyte and kidney function were systematically monitored, and eplerenone doses were adjusted based on renal function and $K^+$ concentration.[21] Numerous registries have reported a large and persistent gap between real-life practice in the use of life-saving evidence-based therapies, such as RAAS inhibitors, beta-blockers, MRAs,[22] and recommended practices in international guidelines in patients with HFrEF,[23] while it is acknowledged that there are varying levels of evidence for goal-directed therapies for HF in the chronic kidney disease population, with a relative paucity of data in patients with advanced chronic kidney disease,[24] who are more prone to experience hyperkalaemia[25] and/or worsening renal function among RAAS inhibitor users. The fear of inducing hyperkalaemia and/or worsening renal function represents the main trigger of this underuse.[26] Of note, the combined use of RAAS inhibitors, loop diuretics and non-steroidal anti-inflammatory drugs in the community increases the risk of developing acute kidney injury.[27] Importantly, a recent US study showed that patients with community acquired acute kidney injury (CA-AKI: 2.5% among 210 895 adults) – as defined by a serum creatinine increase $\geq$0.3 mg/dL or $\geq$ 1.5 times the baseline for consecutive values – were at approximately twofold the risk of *de novo* HF hospitalization (within 90, 180, and 365 days) compared with those who did not have CA-AKI.[28]

There are guideline recommendations for the frequency of $K^+$ monitoring in patients with HF administered a RAAS inhibitor[29] as well as suggestions regarding the frequency of $K^+$ monitoring in patients with hyperkalaemia receiving a $K^+$-lowering agent.[30] Importantly, the present results stemmed from trials where $K^+$ was monitored serially (median number of $K^+$ measurements was 8.2 per patient per year in EPHESUS and 4.5 in EMPHASIS-HF). To ascertain that the performance of our score was not mostly driven by the frequency/number of biological measurements performed during the trial, we performed an interaction analysis. It showed that our score was significantly associated with CV outcomes, regardless of the number of biological measurements made (as assessed by tertile of measurements). However, we identified that the association of the score with CV outcome was strongest in patients with the highest numbers of measurements [HR per 10 point increase in score = 2.05 (1.91–2.19) $P < 0.0001$ in the lowest measurement tertile vs. HR 3.86 (3.34–4.46), $P < 0.0001$ in the highest measurement tertile in EPHESUS]. It should be acknowledged that most biological measurements were performed according to protocol guidelines [i.e. were mainly routine measurements rather than triggered by previous $K^+$ perturbations or worsening clinical status – 11 (9–13) and 8 (5–11) total measurements in EPHESUS and EMPHASIS-HF vs. 10 (8–11) and 7 (5–10) routine/anticipated measurements]. In our view this should be perceived as a strength of our study as the biological monitoring of our patients is in line with current international guidelines but it does limit the generalizability of our results to patients in whom routine systematic biological monitoring is performed, which unfortunately is rare.[31,32] In addition, as the association was strongest in patients with the highest number of available biological measurements the score we propose performs best in patients with the most biological information available.

It is hoped that availability of new safe and well tolerated $K^+$-lowering agents such as the recently approved patiromer and sodium zirconium cyclosilicate will reduce the risks of hyperkalaemia associated with MRA use and potentially could enable the long-term use of MRAs in chronic HF patients despite the occurrence of hyperkalaemia.[24] However, inappropriate use may at least theoretically be associated with more frequent hypokalaemia. Therefore, the long-term risks and benefits of strategies using $K^+$-lowering agents will require adequately powered prospective CV outcome trials.[7] The widespread fear of inducing or worsening hyperkalaemia whilst prescribing or maintaining renin–angiotensin system inhibitors and MRAs is frequently associated with therapeutic inertia. A recent observational study including all Stockholm citizens initiating MRA therapy during 2007–2010 assessed the 1-year incidence of clinical hyperkalaemia, and quantified drug prescription changes after an episode of hyperkalaemia.[33] Within a year, 18.5% of patients experienced at least one detected episode of hyperkalaemia (K+ > 5.0 mmol/L), the majority within the first 3 months of therapy. Development of hyperkalaemia was associated with a four-fold significantly higher risk of mortality overall, while the results were consistent in the subpopulation of patients with HF. After hyperkalaemia, 47% discontinued MRA and only 10% reduced the prescribed dose. Strikingly, when MRA was discontinued, most patients (76%) were not reintroduced to therapy during the subsequent year.

We expect that the present risk score may raise awareness of physicians about the CV risk associated with K+ concentrations outside of the normal range, emphasizes the importance of frequent monitoring and provides a simple tool for adopting strategies for maintaining them in the normal range, rather than discontinuing renin–angiotensin system inhibitors and MRAs, which may not be appropriate. We propose that this easy-to-use score may enable a better physician's use of MRAs and adherence to guidelines, thereby contributing to renewed efforts on education/promotion about these drugs, their indications, and need for follow-up and monitoring.[33]

A prospective study will however be required to establish whether or not the use of this online calculator will help raise awareness and improve decision-making regarding the initiation, maintenance and dose adjustment of renin–angiotensin system inhibitors and MRAs, and $K^+$ binders, and thereby ultimately improve CV outcomes in post-AMI and HF or in chronic HF patients.

## Limitations

First, this was a post-hoc analysis. However, our data were derived from large randomized controlled trials with a rigorous prospective collection of serum creatinine, serum $K^+$, along with clinical parameters, in which clinical events were adjudicated by endpoint committees. Since the $K^+$-derived and MRA intake prediction model was developed and validated in two clinical trial populations, it will necessarily need to be validated in a more generalized community population. Of note, our risk score was developed in populations where most patients were treated with ACEi/ARBs, therefore its generalizability to patients not treated with ACEi/ARBs needs to be confirmed. Our score specifically addresses risk prediction of patients with HFrEF in contrast to the MAGGIC score.[16] A number of variables were considered as time-varying in our models. However, CV risk factors were not re-assessed during the course of the trial. This is a limitation to our analysis. Finally, the recovery of left ventricular function particularly in patients post-AMI was not captured and this could have a strong influence not only on concurrent care but also on the outcomes.

# Conclusions

Adding time-updated variables including $K^+$ concentrations and MRA intake improved the prediction of CV death in patients with HF eligible for renin–angiotensin system inhibitors and MRA therapy. The risk score encompassing repeat $K^+$ concentrations and initiation and discontinuation of MRA therapy may help physicians to better use MRAs, avoid unnecessary and potentially detrimental permanent discontinuations, and therefore improve CV outcomes.

# Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Methods S1.** Supplementary methods.

**Figure S1.** One-year predicted risk of all-cause death as a function of risk score.

**Table S1.** Risk score of all-cause death developed in the EPHESUS cohort and validated in the EMPHASIS-HF cohort.

**Table S2.** Comparison of the performance of our risk scores to the MAGGIC score.

**Table S3.** Distribution of risk score categories across the two trials.

**Table S4.** Assessment of interaction between the number of serum potassium measurements and the value of the prognostic score in Cox models: results in EPHESUS and EMPHASIS-HF.

**Table S5.** Risk score of cardiovascular death – interaction between clinical/biological time-updated variables and the period after measurement (<30 days, ≥30 days).

**Table S6.** Risk score of hospitalization for heart failure – interaction between clinical/biological time-updated variables and the period after measurement (<30 days, ≥30 days).

**Table S7.** Association between time-updated serum potassium and estimated glomerular filtration rate and outcomes, after further adjustment for dose of mineralocorticoid receptor antagonists and loop diuretics during follow-up in the EPHESUS trial.

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