Cardiovascular risk associated with serum potassium in the context of Mineralocorticoid Receptor Antagonist use in patients with heart failure and left ventricular dysfunction.

Patrick Rossignol[1]MD, PhD, Duarte K[1] MSc, Nicolas Girerd MD, PhD [1], Moez Karoui, MD, MSc[1] , JJV. McMurray MD [2], Karl Swedberg MD [3], Dirk J van Veldhuisen MD[4], MSc, Stuart Pocock, PhD [5], Kenneth Dickstein, MD[6], Faiez Zannad, MD, PhD[1], Bertram Pitt, [7,] MD

1. Université de Lorraine, Inserm, Centre d'Investigations Cliniques- Plurithématique 14-33, and Inserm U1116, CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France
2. The British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK
3. Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
4. University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
5. Department of Biostatistics, London School of Hygiene & Tropical Medicine, London, UK.
6. University of Bergen, Stavanger University Hospital, Department of Cardiology, Stavanger, Norway
7. University of Michigan School of Medicine, Ann Arbor, Michigan, USA.

Corresponding author: Pr Patrick Rossignol
Centre d'Investigations Cliniques-INSERM CHRU de Nancy
Institut lorrain du Cœur et des Vaisseaux Louis Mathieu
4 rue du Morvan
54500 Vandoeuvre Lès Nancy
France
Tel : +33 3 83 15 73 20
Fax : +33 3 83 15 73 24
p.rossignol@chru-nancy.fr
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Abstract

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 (AMI) with left ventricular dysfunction (LVSD) or chronic heart failure and reduced left ventricular systolic function (HFrEF)

Methods

Risk scores for predicting cardiovascular (CV) death (primary outcome), hospitalization for heart failure (HHF) and all-cause death were developed. Serum potassium 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 OPTIMAAL (n=5477) and EMPHASIS-HF (chronic HF, n=2737) were used as external validation cohorts.

Findings

The final CV death risk score included medical history, clinical (age, systolic blood pressure, heart rate, BMI, NYHA class) and biological parameters (e.g. K^+, below or above the normal range of 4-5 mmol/L, eGFR, and anemia), 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. A web-based online calculator was created to allow easy determination of the risk score. A sensitivity analysis identified that abnormally high or low values of K^+ carried a particularly high risk for deaths occurring within 30 days.

Interpretation

Adding time-updated variables, including K^+ and MRA treatment, improved risk prediction of CV death in patients with heart failure eligible for RAS 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 CV outcomes, reducing mortality and morbidity in patients with chronic HFrEF or HF after AMI with LVSD

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Introduction

Hypokalemia and hyperkalemia have been consistently shown to be associated with an increased morbidity-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 abnormalities in HF patients receiving RAAS blockers.

Therefore, we have developed a score describing the risk of CV events associated with serum K^+ in patients receiving 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 a reduced ejection fraction and heart failure after acute myocardial infarction (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 (LVSD) (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 background, rationale and results of the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) trial have been previously described [10]. OPTIMAAL was a clinical trial of 5477 patients randomized to losartan (50 mg daily) or captopril (50 mg three times daily) in patients with an AMI and signs or symptoms of HF.

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) study have also been previously reported[11]. In this randomized double-blind trial, 2737 patients with NYHA class II HF and an ejection fraction of no more than 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). Baseline characteristics of these three populations were described using the mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables.

Candidate variables are listed in Online Methods. 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) cardiovascular 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 Methods). Risk score discrimination was assessed using the Harrell's c-index[12]. As described in Ketchum et al.[5], 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 (GOF) test [13].

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, OPTIMAAL and EMPHASIS-HF are presented in Table 1. The median (IQR) follow-up was 16 (12 - 20), 36 (32 - 39) and 21 (10 - 33) months in EPHESUS, OPTIMAAL and EMPHASIS-HF, respectively. The anticipated number of serum K^+ measurements according to the protocol was 10 (8 - 11), 9 (9 - 10) and 7 (5 - 10) in each trial, respectively. The median (IQR) number of actual serum K^+ measurements was 11 (9-13), 9 (7 - 10) 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 potassium measurements per year per patient was 8.2 (7.0 - 10.2), 3.0 (2.8 - 3.2), 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 data supplement Table 1 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, BMI, NYHA class) and biological parameters (e.g. serum potassium, below or above a normal range of 4-5 mmol/L, eGFR, anemia) 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 Figure 1 in the online data supplement 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 the derivation and validation cohorts ranged from 0.78 to 0.80 for EPHESUS and OPTIMAAL 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 both the EPHESUS derivation (p=0.99 for CV death and 0.94 for HF hospitalization) and OPTIMAAL cohorts (p=0.68 and 0.68) at 1 year. In the EMPHASIS-HF cohort, a slight overestimation of predicted risk of CV death was observed at 1 year (p=0.039), which was not the case for hospitalization for HF (p=0.10). At 2 years, the two risk scores were well calibrated in the three cohorts (all p-values > 0.10).

The distribution of risk score categories across the three trials is presented as a supplemental table 2; overall, the OPTIMAAL participants displayed a lower risk profile.

A web-based application was created to allow an easy determination of the complete risk score as a function of available parameters to the physician after 6 months, 1 year and two years. The calculator is available http://recherche-clinique.org/HFcalculator/www/.

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 potassium measurements made during follow-up (using tertiles of potassium measurements - online data supplement Table 3). We identified a significant interaction for all the outcomes examined in EMPHASIS-HF and EPHESUS (all p<0.05 for CVM, HFH and ACM) but not in OPTIMAAL. Overall, the association between the risk score (per 10 points increase) and outcome increased with an increasing number of K^+ measurements in EMPHASIS-HF and EPHESUS. In EPHESUS, the HR for CV death ranged from 2.04 (1.91 - 2.18) in the first tertile of K^+ measurements to 3.72 (3.15 - 4.39) and 3.80 (3.29 - 4.39) in the second and third tertiles. In EMPHASIS-HF the HR for CV death increased from 1.96 (1.67 - 2.30) in the first tertile to 2.94 (2.26 - 3.81) in the third tertile.

Sensitivity analysis

We identified significant interactions between SBP, heart rate, NYHA with the time after measurement (<30 days or 30+ days) for CV death; this was not seen for other variables (online data supplement Table 4). The association between K^+ and CV deaths was as follows: <30 days: HR = 2.55 (1.62 - 4.01) for K>5.5; 30+ days: HR = 1.26 (0.55 - 2.87) for K>5.5 (4-5 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 hyper kalemia were strongly and significantly associated with this outcome <30 days but not for the 30+ days period (<30 days: HR = 2.62 (1.74 - 3.94) for K<3.5, 2.63 (1.73 - 4.00) for K>5.5; 30+ days: HR = 0.86 (0.27-2.71) for K<3.5, 1.39 (0.56-3.44) for K>5.5 – Online data supplement Table 5).

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 LVEF and HF and validated in another high-risk AMI cohort and 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 to previous ones. It is time-updated in contrast with all/most of the previously published risk scores for HF[14-18] . 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 hypokalemia 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 [14], 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 [15], 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 4 other HF treatments including aspirin, beta-blocker, statin, ACEi/ARB. Moreover, medications are accounted for in SPIM only at a single time point. The present risk score was developed using data from a cohort of patients with AMI complicated by a reduced LVEF and HF and validated in another high-risk AMI cohort and in a second, chronic HF, population. This emphasizes its wide applicability to patients with HFrEF regardless of the setting (i.e. de novo ischemic HF, chronic non-ischemic or ischemic 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 January 1, 2000, and December 31, 2008, Goyal et al. 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, irrespectively 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 potassium anytime below or higher than the normal range of 4-5 mmol/L in this post-AMI and LVSD 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 hypokalemia 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 hypokalemia and therefore not take action to maintain normal K^+. Indeed, patients with hypokalemia 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[19]. In the subset of patients with baseline hypokalemia a significantly greater percentage of patients in the eplerenone group exhibited a serum K+ ≥4.0 mmol/L at Month 1 than in the placebo group. A mediation analysis showed that the increase in K^+ above 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) [19]. Conversely, episodes of hyperkalemia or worsening renal function were common in these patients receiving optimal therapy, including ACEi/ARB and β-blockers. The addition of the MRA eplerenone increased the rate of worsening renal function and hyperkalemia. 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 potassium concentration[20]. 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-I, beta blockers, MRAs[21], and recommended practices in international guidelines in patients with HFrEF[22]. The fear of inducing hyperkalemia and/or worsening renal function represents the main trigger of this underuse[23]. Given the high risk of CV death in AMI patients with LVSD and in chronic HF patients with both hypokalemia and hyperkalemia as demonstrated herein, one may also reconsider current recommendations for the monitoring of K^+. There are guideline recommendations for the frequency of K^+ monitoring in patients with HF administered a RAAS-I[24] as well as suggestions regarding the frequency of K^+ monitoring in patients with hyperkalemia receiving a potassium-lowering agent [25]. 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, 3.0 in OPTIMAAL, 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 = 2.04 (1.91 - 2.18) p<0.0001 in the lowest measurement tertile vs HR = 3.80 (3.29 - 4.39) 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), 9 (7 - 10) and 8 (5 - 11) total measurements in EPHESUS, OPTIMAAL and EMPHASIS-HF versus 10 (8 - 11), 9 (9 - 10) 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[26,27]. 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 potassium-lowering agents such as the recently-approved patiromer and sodium zirconium cyclosilicate will reduce the risks of hyperkalemia associated with MRA use and potentially could enable the long-term use of MRAs in chronic HF patients despite the occurrence of hyperkalemia. However, inappropriate use may at least theoretically be associated with more frequent hypokalemia. Therefore, the long-term risks and benefits of strategies using potassium-lowering agents will require adequately powered prospective CV outcome trials[7]. The widespread fear of inducing or worsening hyperkalemia whilst prescribing or maintaining RAS 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 hyperkalemia, and quantified drug prescription changes after an episode of hyperkalemia[28]. Within a year, 18.5% of patients experienced at least one detected episode of hyperkalemia (K+ > 5.0 mmol/L), the majority within the first 3 months of therapy. Development of hyperkalemia 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 hyperkalemia, 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 discontinuating RAS 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[28].

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 RASi and MRAs, and potassium 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 three 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/ARB, therefore its generalizability to patients not

treated with ACEI/ARB needs to be confirmed. Our score specifically addresses risk prediction of patients with HFrEF in contrast to the MAGGIC score [16].

Conclusions

Adding time-updated variables including K^+ concentrations and MRA intake improved the prediction of CV death in patients with HF eligible for RAS 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.

Conflicts of interests

Bertram Pitt: Personal fees (consulting) from Bayer, KBP Pharmaceuticals, AstraZeneca, Merck, Takeda, Relypsa/Vifor, Sanofi, sc Pharmaceuticals , Sarfez pharmaceuticals, Stealth Peptides, and Tricida; stock options from KBP Pharmaceuticals, sc Pharmaceuticals, Sarfez pharmaceuticals, Relypsa, and Tricida; patent for site specific delivery of eplerenone to the myocardium US patent Number 9931412.

Faiez Zannad: Personal fees for Steering Committee membership from Janssen, Bayer, Pfizer, Novartis, Boston Scientific, Resmed, Takeda, General Electric, and Boehringer Ingelheim; consultancy for Amgen, CVRx, Quantum Genomics, Relypsa, ZS Pharma, AstraZeneca, GSK; founder of Cardiovascular Clinical Trialists (CVCT) and of CardioRenal

Patrick Rossignol: Personal fees (consulting) from Novartis, NovoNordisk, Relypsa, AstraZeneca, Grünenthal, Idorsia, Stealth Peptides, Fresenius, Vifor; lecture fees from Bayer and CVRx; cofounder of CardioRenal

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Kenneth Dickstein received remuneration from Merck as member of the OPTIMAAL Executive Steering Committee

All other authors have no conflicts to disclose.

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Tables

Table 1: Baseline characteristics and outcomes of EPHESUS, OPTIMAAL and EMPHASIS-HF patients

	EPHESUS population (N=6632 patients)		OPTIMAAL population (N=5477 patients)		EMPHASIS-HF population (N=2737 patients)	
Characteristics	**N**	**Mean ± SD / n (%)**	**N**	**Mean ± SD / n (%)**	**N**	**Mean ± SD / n (%)**
Age (years)	6632	64 ± 12	5477	67 ± 10	2737	69 ± 8
Gender	6632		5477		2737	
Male		4714 (71.1 %)		3902 (71.2 %)		2127 (77.7 %)
Female		1918 (28.9 %)		1575 (28.8 %)		610 (22.3 %)
Cigarette smoking status	6627		5475		2737	
Never smoker		2587 (39.0 %)		1776 (32.4 %)		1223 (44.7 %)
Current smoker		2043 (30.8 %)		1832 (33.5 %)		293 (10.7 %)
Former smoker		1997 (30.1 %)		1867 (34.1 %)		1221 (44.6 %)
History of alcohol abuse	6615	83 (1.3 %)	5477	21 (0.4 %)	2737	16 (0.6 %)
Body mass index (kg/m²)	6611	27.4 ± 4.5	5279	26.6 ± 3.9	2724	27.5 ± 4.9
Systolic BP (mmHg)	6630	119 ± 16	5441	123 ± 17	2736	124 ± 17
Diastolic BP (mmHg)	6630	72 ± 11	5440	71 ± 11	2736	75 ± 10
Heart Rate (bpm)	6628	75 ± 12	5455	75 ± 14	2735	72 ± 12
Potassium (mmol/L)	6586	4.3 ± 0.4	5229	4.2 ± 0.5	2731	4.3 ± 0.4
eGFR CKD-EPI (mL/min/1.73m²)	6587	68 ± 21	5284	65 ± 17	2725	65 ± 18
Hemoglobin (g/dL)	6556	13.3 ± 1.7	5014	13.4 ± 1.4	2669	13.8 ± 1.6
Anemia	6556	2160 (32.9 %)	5014	1403 (28.0 %)	2669	616 (23.1 %)
Medical history						
Previous MI	6632	1802 (27.2 %)	5477	998 (18.2 %)	2734	1380 (50.5 %)
Atrial fibrillation	6632	874 (13.2 %)	5477	562 (10.3 %)	2737	844 (30.8 %)
Renal insufficiency	6632	434 (6.5 %)	5477	118 (2.2 %)	2737	214 (7.8 %)
COPD	6632	625 (9.4 %)	5477	293 (5.3 %)	2734	391 (14.3 %)
Heart failure	6632	975 (14.7 %)	5477	339 (6.2 %)	2734	1438 (52.6 %)
Hypertension	6632	4007 (60.4 %)	5477	1970 (36.0 %)	2737	1819 (66.5 %)
Diabetes	6632	2142 (32.3 %)	5477	940 (17.2 %)	2737	859 (31.4 %)
Peripheral vascular disease	6632	823 (12.4 %)	5477	140 (2.6 %)	2737	94 (3.4 %)
Medication						
Any diuretic use	6632	3984 (60.1 %)	5477	3496 (63.8 %)	2721	2326 (85.5 %)
Beta-blocker use	6632	4961 (74.8 %)	5477	4306 (78.6 %)	2721	2374 (87.2 %)
ACEI use	6632	5616 (84.7 %)	5477	0 (0.0 %)*	2721	2124 (78.1 %)
ARB use	6632	216 (3.3 %)	5477	0 (0.0 %)*	2721	527 (19.4 %)
ACEI / ARB use	6632	5751 (86.7 %)	5477	0 (0.0 %)*	2721	2558 (94.0 %)
Study treatment	6632		5477		2737	
Placebo		3313 (50.0 %)		0 (0.0 %)		1373 (50.2 %)
Eplerenone		3319 (50.0 %)		0 (0.0 %)		1364 (49.8 %)
Captopril		0 (0.0 %)		2733 (49.9 %)		0 (0.0 %)
Losartan		0 (0.0 %)		2744 (50.1 %)		0 (0.0 %)
Study treatment taken or not at baseline	6632		5477		2737	
Not taken		24 (0.4 %)		31 (0.6 %)		7 (0.3 %)
Taken		6608 (99.6 %)		5446 (99.4 %)		2730 (99.7 %)
Outcomes						
All-cause death	6632	1032 (15.6 %)	5477	946 (17.3 %)	2737	384 (14.0 %)
CV death	6632	890 (13.4 %)	5477	783 (14.3 %)	2737	332 (12.1 %)
Hospitalization for HF	6632	855 (12.9 %)	5477	571 (10.4 %)	2737	417 (15.2 %)
CV death / Hospitalization for HF	6632	1451 (21.9 %)	5477	1153 (21.1 %)	2737	605 (22.1 %)

N: number of non-missing values; SD: standard deviation; BP: blood pressure; MI: myocardial infarction; COPD: chronic obstructive percutaneous disease; ACEI: angiotensin converting enzyme inhibitor; ARB: antagonist receptor blocker; HF: heart failure; CV: cardiovascular * at randomization ; 50% ACEI/50% ARB per randomisation

Table 2: Risk scores of CV death and hospitalization for HF developed in the EPHESUS cohort and validated in the OPTIMAAL and EMPHASIS-HF cohorts

Variables	CV death				Hospitalization for HF			
	HR (CI 95 %)	p-value	β	Points	HR (CI 95 %)	p-value	β	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 (1.05 - 1.62)	0.018	0.26	3	1.00 (0.79 - 1.27)	1.00	0.00	0
> 5.5	2.09 (1.40 - 3.11)	0.0003	0.74	7	2.22 (1.51 - 3.25)	<0.0001	0.80	8
eGFR CKD-EPI (mL/min/1.73m²)								
< 30	2.61 (1.83 - 3.73)	<0.0001	0.96	10	2.26 (1.59 - 3.23)	<0.0001	0.82	8
30 - 44	1.76 (1.28 - 2.41)	0.0005	0.56	6	2.12 (1.60 - 2.81)	<0.0001	0.75	7
45 - 59	1.32 (0.98 - 1.79)	0.069	0.28	3	1.53 (1.16 - 2.00)	0.002	0.42	4
60 - 89	1.18 (0.89 - 1.56)	0.25	0.16	2	1.09 (0.84 - 1.42)	0.50	0.09	1
≥ 90	1.00	-	-	0	1.00	-	-	0
Anemia	1.20 (1.03 - 1.40)	0.019	0.18	2	1.76 (1.52 - 2.05)	<0.0001	0.57	6
Body mass index (kg/m²)								
< 18.5	1.69 (1.01 - 2.81)	0.044	0.52	5	-	-	-	-
18.5 - 24.9	1.34 (1.14 - 1.58)	0.0004	0.29	3	-	-	-	-
25 - 29.9	1.00	-	-	0	-	-	-	-
≥ 30	1.04 (0.86 - 1.26)	0.67	0.04	0	-	-	-	-
Systolic BP (mmHg)								
< 100	3.10 (2.42 - 3.97)	<0.0001	1.13	11	1.99 (1.50 - 2.64)	<0.0001	0.69	7
100 - 119	1.50 (1.22 - 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)	0.14	0.15	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	3.20 (2.23 - 4.59)	<0.0001	1.16	12	4.04 (2.63 - 6.19)	<0.0001	1.40	14
NYHA class								
I	1.00	-	-	0	1.00	-	-	0
II	1.23 (1.00 - 1.51)	0.047	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	2.87 (2.33 - 3.55)	<0.0001	1.06	11
Permanent discontinuation of study treatment	1.67 (1.38 - 2.01)	<0.0001	0.51	5	-	-	-	-
Fixed variables (baseline)								
Age (years)								
< 65	1.00	-	-	0	-	-	-	-
65 - 74	1.25 (1.04 - 1.51)	0.018	0.23	2	-	-	-	-
≥ 75	1.34 (1.09 - 1.65)	0.006	0.29	3	-	-	-	-
Previous MI	1.25 (1.06 - 1.46)	0.006	0.22	2	1.38 (1.18 - 1.61)	<0.0001	0.32	3
Atrial fibrillation	1.26 (1.06 - 1.50)	0.009	0.23	2	1.23 (1.03 - 1.46)	0.024	0.20	2
History of heart failure	1.26 (1.06 - 1.50)	0.011	0.23	2	1.25 (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 - 1.61)	0.001	0.29	3	1.37 (1.14 - 1.64)	0.0006	0.31	3
Any diuretic use	1.30 (1.09 - 1.55)	0.003	0.27	3	1.67 (1.39 - 1.99)	<0.0001	0.51	5
No beta-blocker use	1.35 (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 (CI 95 %)								
Derivation (EPHESUS)	0.783 (0.763 - 0.804)				0.781 (0.760 - 0.802)			
Validation (OPTIMAAL)	0.800 (0.774 - 0.826)				0.773 (0.744 - 0.802)			
Validation (EMPHASIS-HF)	0.749 (0.715 - 0.783)				0.742 (0.712 - 0.772)			

BP: blood pressure; MI: myocardial infarction; CV: cardiovascular; HR: hazard ratio; CI: confidence interval; β: regression coefficient.

Figures

Figure 1: 1-year predicted risk of CV death and hospitalization for HF as a function of risk score

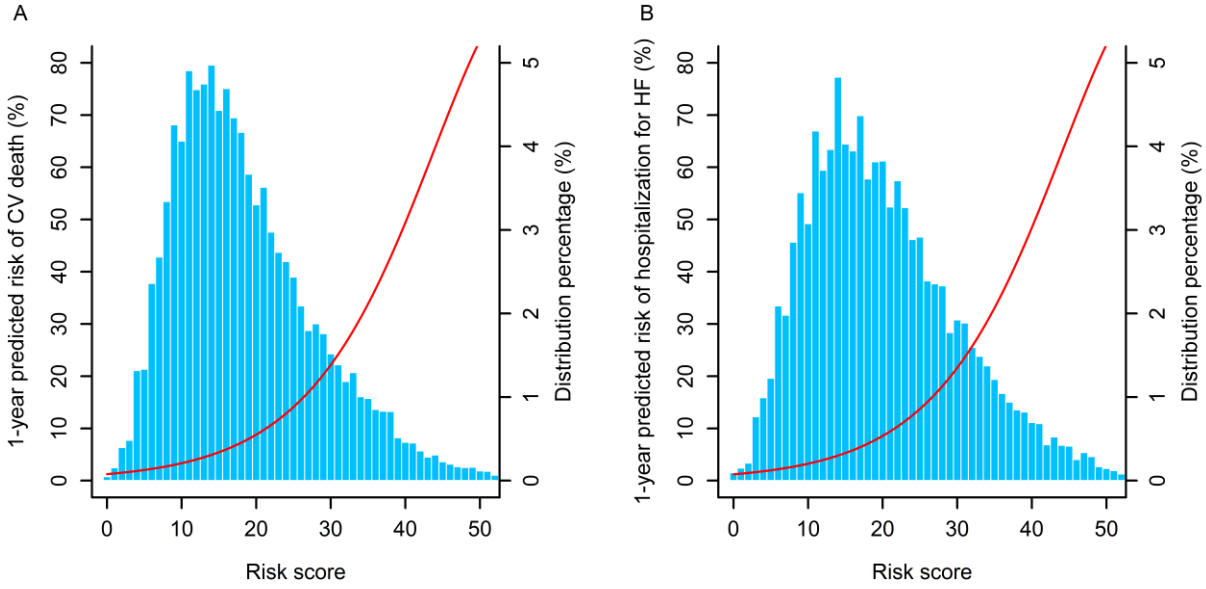
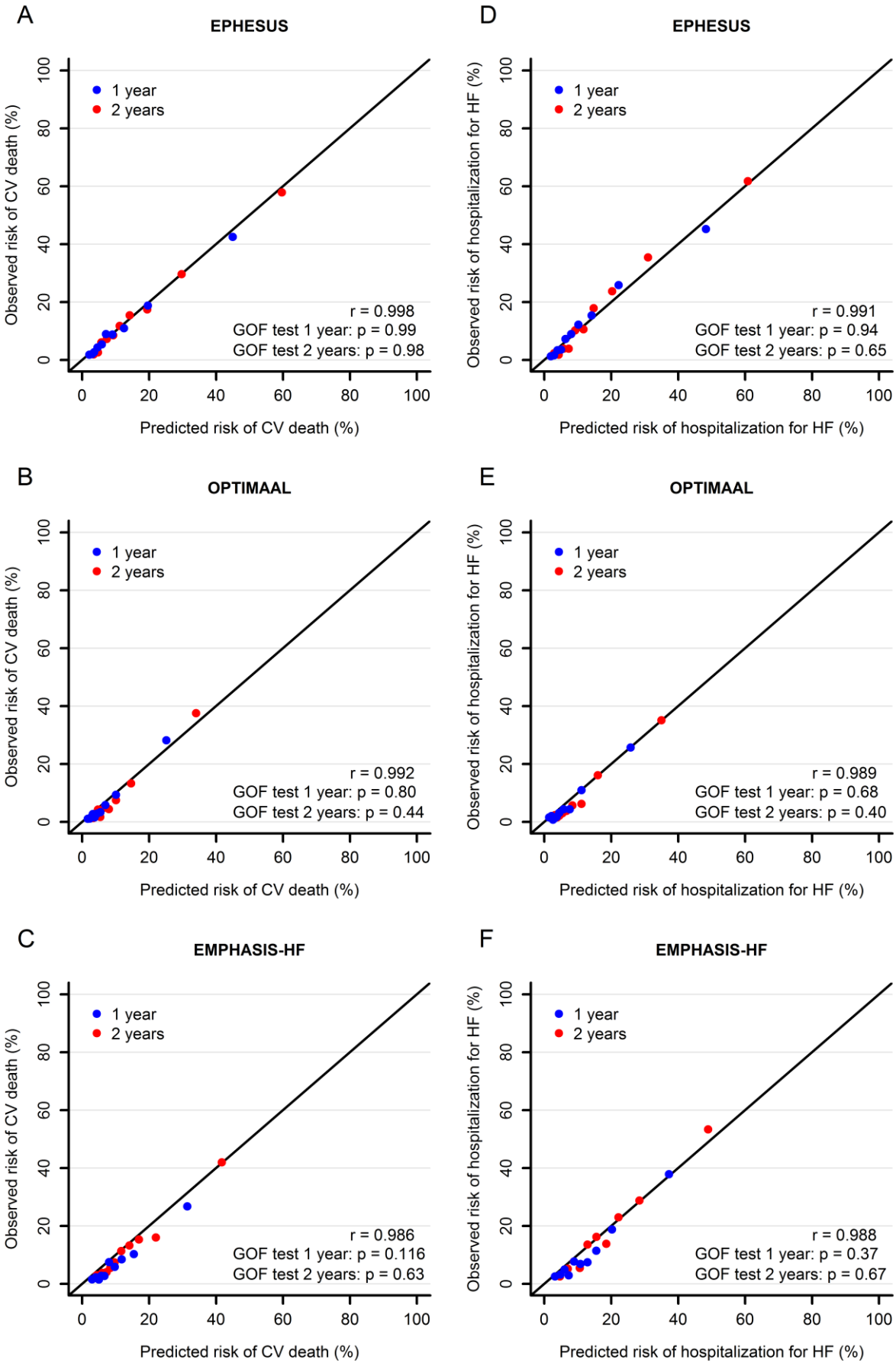


Figure 2: Predicted risk *versus* observed risk by deciles of risk score in the EPHESUS derivation cohort (A, D) and OPTIMAAL (B, E) and EMPHASIS-HF (C, F) validation cohorts



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Online data supplements

Online Methods

Candidate variables

Candidate variables included: age, gender, smoking status, alcohol abuse, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, potassium, medical history (previous MI, atrial fibrillation, renal insufficiency, chronic obstructive pulmonary disease (COPD), heart failure, hypertension, diabetes, peripheral vascular disease) and medication use (any diuretic, beta-blocker, ACEI and/or ARB, study drug with placebo/eplerenone for EPHESUS and EMPHASIS-HF, captopril/losartan for OPTIMAAL, permanent discontinuation of study drug). Several derived variables, such as body mass index (BMI), anemia defined according to the World Health Organization (WHO) criteria as a hemoglobin <13 g/dl for men and <12 g/dl for women and estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI formula[29], were also considered.

The last candidate variable was NYHA class. In the EMPHASIS-HF trial, the NYHA class was assessed at baseline which was not the case in the two others trials where patients were included after AMI. NYHA class was measured for the first time at week 1 in the EPHESUS trial and at month 1 in the OPTIMAAL trial. In order to take into account this key clinical tool to construct the risk scores, it was decided to consider only the patients of each cohort who underwent a NYHA class measurement within the first 90 days of follow-up to avoid the loss of data from contributing patients mainly in the OPTIMAAL trial. The new start date for the follow-up was hence defined as being the first date of NYHA class assessment.

In the three clinical trials, laboratory and clinical parameters were regularly measured during follow-up. The following variables were considered as time-updated covariates with multiple changes: potassium, anemia, eGFR, NYHA class, SBP, DBP, heart rate, BMI. Permanent discontinuation of the study drug was used as a time-updated covariate with unique change. A patient was considered as having permanently discontinued the study drug if he or she never started the study medication or if he or she ceased taking study drug and was followed in the

trial at least 7 days after this discontinuation date. All other variables were considered as static covariates available at baseline.

As the present objective was to create "simplified" risk scores, all continuous variables were categorized using established clinical thresholds from the literature. For example, potassium was classified in 5 categories: severe hypokalemia (<3.5 mmol/L), moderate hypokalemia (3.5-3.9 mmol/L), normal kalemia (4-5 mmol/L), moderate hyperkalemia (5.1-5.5 mmol/L) and severe hyperkalemia (>5.5 mmol/L)[19,20,30].

Predicted risk calculation

The predicted risk of event for a patient at time point $\boldsymbol{t}$ was calculated using the following equation:

$$\boldsymbol{R(t) = 1 - (BaselineSurvival(t))^{e^{score/10}}}$$

The term $\boldsymbol{BaselineSurvival(t)}$ (baseline survival function for a patient with a score of 0 at time point **t**) was estimated at 6 months, 1 year and 2 years in the derivation cohort (EPHESUS) using the function “basehaz” of the "survival" R package, and subsequently used to calculate predicted risk for each patient.

Table 1: Risk score of all-cause death developed in the EPHESUS cohort and validated in the OPTIMAAL and EMPHASIS-HF cohorts

Variables	All-cause death			
	HR (CI 95 %)	p-value	β	Points
Time-updated variables				
Potassium (mmol/L)				
< 3.5	2.23 (1.64 - 3.02)	<0.0001	0.80	8
3.5 - 3.9	1.32 (1.08 - 1.60)	0.007	0.27	3
4 - 5	1.00	-	-	0
5.1 - 5.5	1.35 (1.11 - 1.65)	0.003	0.30	3
> 5.5	1.93 (1.33 - 2.78)	0.0005	0.66	7
eGFR CKD-EPI (mL/min/1.73m²)				
< 30	3.02 (2.17 - 4.21)	<0.0001	1.11	11
30 - 44	1.84 (1.37 - 2.47)	<0.0001	0.61	6
45 - 59	1.40 (1.06 - 1.86)	0.019	0.34	3
60 - 89	1.24 (0.96 - 1.61)	0.10	0.22	2
≥ 90	1.00	-	-	0
Anemia	1.26 (1.09 - 1.45)	0.001	0.23	2
Body mass index (kg/m²)				
< 18.5	1.98 (1.26 - 3.10)	0.003	0.68	7
18.5 - 24.9	1.35 (1.16 - 1.57)	<0.0001	0.30	3
25 - 29.9	1.00	-	-	0
≥ 30	1.01 (0.84 - 1.21)	0.93	0.01	0
Systolic BP (mmHg)				
< 100	2.87 (2.28 - 3.60)	<0.0001	1.05	11
100 - 119	1.37 (1.13 - 1.66)	0.001	0.32	3
120 - 139	1.13 (0.94 - 1.36)	0.20	0.12	1
≥ 140	1.00	-	-	0
Heart rate (bpm)				
≤ 60	1.00	-	-	0
61 - 80	1.09 (0.89 - 1.33)	0.39	0.09	1
81 - 100	1.81 (1.45 - 2.25)	<0.0001	0.59	6
> 100	3.38 (2.44 - 4.70)	<0.0001	1.22	12
NYHA class				
I	1.00	-	-	0
II	1.25 (1.03 - 1.51)	0.021	0.22	2
III/IV	3.24 (2.66 - 3.96)	<0.0001	1.18	12
Permanent discontinuation of study treatment	1.97 (1.67 - 2.32)	<0.0001	0.68	7
Fixed variables (baseline)				
Age (years)				
< 65	1.00	-	-	0
65 - 74	1.24 (1.04 - 1.48)	0.014	0.22	2
≥ 75	1.33 (1.10 - 1.62)	0.004	0.29	3
Male	1.18 (1.02 - 1.37)	0.027	0.17	2
Previous MI	1.22 (1.05 - 1.41)	0.009	0.20	2
Atrial fibrillation	1.21 (1.03 - 1.43)	0.020	0.19	2
History of heart failure	1.24 (1.05 - 1.46)	0.011	0.21	2
Diabetes	1.22 (1.07 - 1.41)	0.004	0.20	2
Peripheral vascular disease	1.31 (1.10 - 1.55)	0.002	0.27	3
Any diuretic use	1.20 (1.02 - 1.40)	0.026	0.18	2
No beta-blocker use	1.38 (1.20 - 1.58)	<0.0001	0.32	3
Study treatment				
Eplerenone	0.84 (0.74 - 0.96)	0.011	-0.17	0
Placebo/Not on eplerenone	1.00	-	-	2
C-index (CI 95 %)				
Derivation (EPHESUS)	0.791 (0.772 - 0.810)			
Validation (OPTIMAAL)	0.805 (0.782 - 0.829)			
Validation (EMPHASIS-HF)	0.755 (0.723 - 0.786)			

Table 2: Distribution of risk score categories across the three trials

Outcome	Risk categories	EPHESUS	OPTIMAAL	EMPHASIS-HF
CV death	Low risk (0-11)	12765 (20.4%)	13302 (36.0%)	1228 (5.8%)
	Midly risk (12-20)	25375 (40.6%)	15880 (43.0%)	10214 (47.9%)
	Moderately risk (21-27)	12291 (19.7%)	4774 (12.9%)	6476 (30.4%)
	Highly risk (28-86)	12062 (19.3%)	2980 (8.1%)	3399 (15.9%)
Hospitalization for HF	Low risk (0-10)	8567 (15.0%)	10968 (31.5%)	556 (2.8%)
	Midly risk (11-19)	21581 (37.7%)	14863 (42.7%)	5972 (29.6%)
	Moderately risk (20-26)	13608 (23.8%)	5787 (16.6%)	7468 (37.1%)
	Highly risk (27-76)	13470 (23.5%)	3158 (9.1%)	6156 (30.5%)

Cox models with time-updated covariates were used for constructing risk scores. Hence multiple observations per patient were used, with starting and stopping time for each observation. Data are expressed as number of observations (percentage).

Table 3: Assessment of interaction between the number of serum potassium measurements (NK^+) and the value of the prognostic score in Cox models: results in EPHESUS, OPTIMAAL and EMPHASIS-HF

Variables	Outcome = CV death		Outcome = Hosp. for HF		Outcome = All-cause death	
	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value
EPHESUS						
Effect of score depending of NK^+						
1st tertile of number of serum potassium measurements						
Score (per 10 pts)	2.04 (1.91 - 2.18)	<0.0001	2.25 (2.09 - 2.42)	<0.0001	2.00 (1.88 - 2.12)	<0.0001
2nd tertile of number of serum potassium measurements						
Score (per 10 pts)	3.72 (3.15 - 4.39)	<0.0001	3.87 (3.24 - 4.62)	<0.0001	3.70 (3.20 - 4.28)	<0.0001
3rd tertile of number of serum potassium measurements						
Score (per 10 pts)	3.80 (3.29 - 4.39)	<0.0001	2.97 (2.46 - 3.58)	<0.0001	3.50 (3.11 - 3.92)	<0.0001
Interaction Tertiles x Score		<0.0001		<0.0001		<0.0001
OPTIMAAL						
Effect of score depending of NK^+						
1st tertile of number of serum potassium measurements						
Score (per 10 pts)	2.44 (2.25 - 2.63)	<0.0001	2.19 (1.99 - 2.41)	<0.0001	2.34 (2.18 - 2.50)	<0.0001
2nd tertile of number of serum potassium measurements						
Score (per 10 pts)	2.56 (1.83 - 3.58)	<0.0001	3.04 (1.78 - 5.16)	<0.0001	2.91 (2.25 - 3.77)	<0.0001
3rd tertile of number of serum potassium measurements						
Score (per 10 pts)	3.18 (2.06 - 4.92)	<0.0001	2.57 (1.24 - 5.30)	0.011	3.20 (2.15 - 4.74)	<0.0001
Interaction Tertiles x Score		0.48		0.46		0.096
EMPHASIS-HF						
Effect of score depending of NK^+						
1st tertile of number of serum potassium measurements						
Score (per 10 pts)	1.96 (1.67 - 2.30)	<0.0001	2.23 (1.92 - 2.60)	<0.0001	1.89 (1.64 - 2.18)	<0.0001
2nd tertile of number of serum potassium measurements						
Score (per 10 pts)	2.51 (2.06 - 3.07)	<0.0001	2.92 (2.33 - 3.66)	<0.0001	2.40 (2.03 - 2.83)	<0.0001
3rd tertile of number of serum potassium measurements						
Score (per 10 pts)	2.94 (2.26 - 3.81)	<0.0001	3.20 (2.32 - 4.42)	<0.0001	2.74 (2.20 - 3.42)	<0.0001
Interaction Tertiles x Score		0.018		0.045		0.010

Tertiles were the following:
1st tertile: ≤ 9 measures, 2nd tertile: 10-12 measures, 3rd tertile: ≥ 13 measures for all outcomes in EPHESUS,
1st tertile: ≤ 8 measures, 2nd tertile: 9 measures, 3rd tertile: ≥ 10 measures for all outcomes in OPTIMAAL,
And 1st tertile: ≤ 6 measures, 2nd tertile: 7-10 measures, 3rd tertile: ≥ 11 measures for mortality outcomes and
1st tertile: ≤ 5 measures, 2nd tertile: 6-9 measures, 3rd tertile: ≥ 9 measures for HF hospitalization for EMPHASIS-HF.

Table 4: Risk score of CV death

	< 30 days after measurement			≥ 30 days after measurement			Interaction
	$N_{events*}$	HR (CI 95 %)	p-value	$N_{events*}$	HR (CI 95 %)	p-value	p-value
Time-updated variables							
Potassium (mmol/L)	490			298			0.36
< 3.5	27	2.37 (1.58 - 3.54)	<0.0001	11	1.65 (0.90 - 3.06)	0.11	
3.5 - 3.9	66	1.29 (0.99 - 1.69)	0.064	36	1.21 (0.85 - 1.73)	0.29	
4 - 5	311	1.00	-	214	1.00	-	
5.1 - 5.5	65	1.46 (1.11 - 1.91)	0.006	31	1.06 (0.73 - 1.56)	0.75	
> 5.5	21	2.55 (1.62 - 4.01)	<0.0001	6	1.26 (0.55 - 2.87)	0.59	
eGFR CKD-EPI (mL/min/1.73m²)	388			400			0.25
< 30	58	2.93 (1.83 - 4.68)	<0.0001	33	1.81 (1.08 - 3.04)	0.024	
30 – 44	89	1.81 (1.18 - 2.78)	0.007	94	1.67 (1.09 - 2.55)	0.018	
45 – 59	90	1.34 (0.88 - 2.04)	0.17	95	1.32 (0.88 - 2.00)	0.18	
60 – 89	119	1.12 (0.75 - 1.66)	0.58	145	1.26 (0.86 - 1.86)	0.23	
≥ 90	32	1.00	-	33	1.00	-	
Anemia	388			400			
No	219	1.00	-	252	1.00	-	
Yes	169	1.13 (0.91 - 1.39)	0.27	148	1.30 (1.05 - 1.62)	0.016	0.34
Body mass index (kg/m²)	401			387			0.33
< 18.5	5	0.90 (0.37 - 2.22)	0.83	11	2.52 (1.34 - 4.73)	0.004	
18.5 - 24.9	157	1.28 (1.02 - 1.60)	0.033	151	1.36 (1.08 - 1.71)	0.010	
25 - 29.9	154	1.00	-	143	1.00	-	
≥ 30	85	1.02 (0.78 - 1.33)	0.88	82	1.03 (0.78 - 1.36)	0.82	
Systolic BP (mmHg)	438			350			0.013
< 100	91	4.35 (3.10 - 6.09)	<0.0001	39	1.85 (1.25 - 2.74)	0.002	
100 – 119	149	1.82 (1.35 - 2.46)	0.0001	111	1.25 (0.94 - 1.66)	0.13	
120 – 139	135	1.44 (1.07 - 1.95)	0.018	112	0.97 (0.74 - 1.29)	0.85	
≥ 140	63	1.00	-	88	1.00	-	
Heart rate (bpm)	439			349			0.019
≤ 60	55	1.00	-	54	1.00	-	
61 – 80	220	1.10 (0.82 - 1.48)	0.53	204	1.07 (0.79 - 1.44)	0.68	
81 – 100	130	2.07 (1.50 - 2.87)	<0.0001	81	1.46 (1.03 - 2.08)	0.035	
> 100	34	4.21 (2.69 - 6.61)	<0.0001	10	1.46 (0.74 - 2.91)	0.28	
NYHA class	446			342			0.018
I	65	1.00	-	71	1.00	-	
II	149	1.24 (0.93 - 1.67)	0.15	155	1.29 (0.97 - 1.71)	0.084	
III/IV	232	3.81 (2.84 - 5.11)	<0.0001	116	2.49 (1.82 - 3.42)	<0.0001	
Permanent discontinuation of study treatment		1.90 (1.57 - 2.30)	<0.0001		1.90 (1.57 - 2.30)	<0.0001	-
Fixed variables (baseline)							
Age (years)							-
< 65		1.00	-		1.00	-	
65 - 74		1.22 (1.01 - 1.48)	0.037		1.22 (1.01 - 1.48)	0.037	
≥ 75		1.36 (1.10 - 1.67)	0.004		1.36 (1.10 - 1.67)	0.004	
Previous MI		1.24 (1.05 - 1.45)	0.009		1.24 (1.05 - 1.45)	0.009	-
Atrial fibrillation		1.24 (1.04 - 1.47)	0.017		1.24 (1.04 - 1.47)	0.017	-
History of heart failure		1.20 (1.00 - 1.43)	0.048		1.20 (1.00 - 1.43)	0.048	-
Diabetes		1.22 (1.05 - 1.42)	0.010		1.22 (1.05 - 1.42)	0.010	-
Peripheral vascular disease		1.33 (1.11 - 1.59)	0.002		1.33 (1.11 - 1.59)	0.002	-
Any diuretic use		1.30 (1.09 - 1.55)	0.003		1.30 (1.09 - 1.55)	0.003	-
No beta-blocker use		1.31 (1.13 - 1.52)	0.0004		1.31 (1.13 - 1.52)	0.0004	-
Study treatment							-
Eplerenone		0.83 (0.72 - 0.95)	0.008		0.83 (0.72 - 0.95)	0.008	
Placebo/Not on eplerenone		1.00	-		1.00	-	

* The number of patients having the event in each category was only given for the time-updated variables, assessed within 30 days after measurement and ≥30 days after measurement.

Table 5: Risk score of hospitalization for HF

	< 30 days after measurement			≥ 30 days after measurement			Interaction
	$N_{events*}$	HR (CI 95 %)	p-value	$N_{events*}$	HR (CI 95 %)	p-value	p-value
Time-updated variables							
Potassium (mmol/L)	563			214			0.033
< 3.5	25	2.62 (1.74 - 3.94)	<0.0001	3	0.86 (0.27 - 2.71)	0.80	
3.5 - 3.9	90	1.67 (1.32 - 2.11)	<0.0001	19	0.94 (0.58 - 1.51)	0.80	
4 – 5	373	1.00	-	161	1.00	-	
5.1 - 5.5	51	0.90 (0.67 - 1.21)	0.50	26	1.16 (0.77 - 1.76)	0.48	
> 5.5	24	2.63 (1.73 - 4.00)	<0.0001	5	1.39 (0.56 - 3.44)	0.48	
eGFR CKD-EPI (mL/min/1.73m²)	412			365			0.80
< 30	33	1.88 (1.18 - 3.01)	0.008	30	2.73 (1.62 - 4.63)	0.0002	
30 – 44	95	1.79 (1.23 - 2.59)	0.002	90	2.40 (1.57 - 3.67)	<0.0001	
45 – 59	108	1.33 (0.93 - 1.90)	0.12	95	1.76 (1.16 - 2.67)	0.008	
60 – 89	133	0.94 (0.66 - 1.33)	0.72	120	1.31 (0.87 - 1.95)	0.19	
≥ 90	43	1.00	-	30	1.00	-	
Anemia	412			365			
No	217	1.00	-	219	1.00	-	
Yes	195	1.82 (1.49 - 2.22)	<0.0001	146	1.69 (1.35 - 2.10)	<0.0001	0.63
Systolic BP (mmHg)	461			316			0.76
< 100	49	1.92 (1.34 - 2.74)	0.0003	25	1.73 (1.09 - 2.75)	0.020	
100 – 119	172	1.51 (1.17 - 1.94)	0.002	104	1.53 (1.13 - 2.06)	0.005	
120 – 139	140	0.99 (0.76 - 1.28)	0.93	109	1.15 (0.86 - 1.54)	0.34	
≥ 140	100	1.00	-	78	1.00	-	
Heart rate (bpm)	459			318			0.088
≤ 60	55	1.00	-	36	1.00	-	
61 – 80	248	1.21 (0.91 - 1.63)	0.19	192	1.57 (1.10 - 2.24)	0.013	
81 – 100	133	2.23 (1.62 - 3.07)	<0.0001	85	2.67 (1.80 - 3.96)	<0.0001	
> 100	23	5.07 (3.10 - 8.31)	<0.0001	5	1.96 (0.77 - 5.01)	0.16	
NYHA class	462			315			0.007
I	72	1.00	-	76	1.00	-	
II	194	1.45 (1.10 - 1.90)	0.008	152	1.11 (0.84 - 1.47)	0.45	
III/IV	196	3.74 (2.82 - 4.96)	<0.0001	87	1.96 (1.42 - 2.70)	<0.0001	
Fixed variables (baseline)							
Previous MI		1.34 (1.15 - 1.57)	0.0002		1.34 (1.15 - 1.57)	0.0002	-
Atrial fibrillation		1.21 (1.02 - 1.45)	0.032		1.21 (1.02 - 1.45)	0.032	-
History of heart failure		1.22 (1.03 - 1.46)	0.024		1.22 (1.03 - 1.46)	0.024	-
Hypertension		1.32 (1.12 - 1.55)	0.0009		1.32 (1.12 - 1.55)	0.0009	-
Diabetes		1.23 (1.06 - 1.43)	0.006		1.23 (1.06 - 1.43)	0.006	-
Peripheral vascular disease		1.36 (1.14 - 1.63)	0.0008		1.36 (1.14 - 1.63)	0.0008	-
Any diuretic use		1.66 (1.39 - 1.99)	<0.0001		1.66 (1.39 - 1.99)	<0.0001	-
Study treatment							-
Eplerenone		0.81 (0.71 - 0.94)	0.005		0.81 (0.71 - 0.94)	0.005	
Placebo/Not on eplerenone		1.00	-		1.00	-	

* The number of patients having the event in each category was only given for the time-updated variables, assessed within 30 days after measurement and ≥30 days after measurement.

Figure 1: 1-year predicted risk of all-cause death as a function of risk score