**Supplementary Material**

**Development of a health economic model to evaluate the potential benefits of optimal serum potassium management in patients with heart failure**

## Methods to model heart failure progression and events

Table S1. Summary of methods employed to model disease progression and events in heart failure patients

|  |  |  |  |
| --- | --- | --- | --- |
| **Events** | **Baseline incidence rate** | **Modified by RAASi use?** | **Modified by K+ levels?** |
| Progression (NYHA) | Yao et al.1 | ✓ | Appropriate data not identified | 🗶 |  |
| Acute hyperkalemia  | Incidence of K+ above threshold | 🗶 |  | ✓ | By definition |
| RAASi discontinuation | By dose; Epstein et al.2 | ✓ | By definition | ✓ | By K+ category; Epstein et al.2 |
| RAASi down-titration | By dose; Epstein et al.2 | ✓ | By definition | ✓ | By K+ category; Epstein et al.2 |
| Arrhythmia | Monthly probability; Colquitt et al.3 | 🗶 |  | ✓ | Assumed same as CKD; Luo et al.4 |
| Hospitalization | By NYHA class; Ford et al.5 | ✓ | OR any versus none; Flather et al.6 | ✓ | Assumed same as CKD; Luo et al.4 |
| Mortality\* | By NYHA class and other risk factors; SHFM7 | ✓ | Any versus none; Risk factor in SHFM7 | ✓ | HR by K+ category; Krogager et al.8 |
| *CKD: chronic kidney disease; HR: hazard ratio; IRR: incidence rate ratio, K+: potassium; NYHA: New York Heart Association; OR: odds ratio; RAASi: renin-angiotensin-aldosterone system inhibitor; SHFM: Seattle Heart Failure Model; ✓: functionality; 🗶: no functionality (due to paucity of identified data)*\*The higher probability based on (A) comorbidity, RAASi use and K+ levels or (B) life tables is applied throughout |

## Estimating serum potassium profiles within the health economic model

Time-dependent serum potassium (K+) trajectories were modelled at the patient-level using mixed-effects regression models. The mixed effects models used to estimate potassium trajectories take the form:

$$K\_{ij}^{+}=\left(α+υ\_{i}\right)+\sum\_{k}^{}\left(β\_{k}+γ\_{ik}\right)×Time\_{ijk}+ε\_{ij}$$

$$υ\_{i} \~ N\left(0,σ\_{υ\_{i}}^{2}\right) ; γ\_{ik} \~ N\left(0,σ\_{γ\_{ik}}^{2}\right) for each k ; ε\_{ij }\~ N(0,σ\_{ε\_{ij}}^{2})$$

Where $K\_{ij}^{+}$ represents a potassium measurement for patient $i$ made at time $j$; $Time\_{ijk}$ is a time index of specification $k$, representing patient $i$‘s time at measurement occasion $j$; $α$ and $β\_{k}$ are fixed intercept and slope coefficients respectively, representing population-averaged baseline potassium concentration and the association between potassium and time; $υ\_{i}$ and $γ\_{ik}$ are random intercept and slope terms respectively, representing patient-specific effects for patient $i$ (allowing levels and slopes of potassium trajectories to vary by patient); and $ε\_{ij}$ is a random error term for patient $i$ at measurement occasion $j$, capturing all sources of variation in potassium not explained by the model.

The measurement-level (level 1) random error term $ε\_{ij}$ is assumed to be normally distributed with mean 0 and constant variance $σ\_{ε\_{ij}}^{2}$. Like $ε\_{ij}$, $υ\_{i}$ and $γ\_{ik}$ are error terms with constant patient-level (level 2) variances $σ\_{υ\_{i}}^{2}$ and $σ\_{γ\_{ik}}^{2}$ respectively; it is these patient-level variances that must be estimated in the model to provide estimates of the random effects, in contrast to $α$ and $β\_{k}$ which are global coefficients to be estimated to provide estimates of the fixed effects. The total variance in potassium about the population-averaged time trend is equal to the sum of the individual level 1 and level 2 variance components, $σ^{2}=σ\_{υ\_{i}}^{2}+\sum\_{k}^{}σ\_{γ\_{ik}}^{2}+σ\_{ε\_{ij}}^{2}$. All else being equal: larger values of $σ\_{υ\_{i}}^{2}$ will increase the spread of patient-specific mean values about the global time trend; larger values of $σ\_{γ\_{ik}}^{2}$ will increase the spread of the slopes of patient-specific time trends; and larger values of $σ\_{ε\_{ij}}^{2}$ will increase the spread of measured K+ values about patient-specific time trends.

Note: In the model application presented in the main body of the article serum potassium levels of 4.5 mEq/L were modelled, representing maintained normokalemia.

## Baseline patient characteristic inputs

Baseline parameters required by the health economic model to inform risk calculations are summarized in Table S2. Where available, input values for each variable were derived from a previous analysis of a cohort of 23,541 heart failure patients listed in the UK Clinical Practice Research Datalink (CPRD) between January 2006 and December 20159. If the variable was not included in that CPRD analysis, inputs were consistent with the baseline profile of the Seattle Heart Failure Model derivation cohort7. This approach was deemed appropriate, in the absence of available data, since the variables for which CPRD results were not available impact the prediction of mortality risk via the Seattle Heart Failure Model only.

Table S2. Baseline patient characteristics applied in model analyses

|  |  |  |
| --- | --- | --- |
| **Baseline characteristic** | **Input value** | **Source** |
| Age (years) | 73 | CPRD |
| Proportion female  | 0.43 |
| eGFR (mL/min/1.73m2) | 67 |
| Proportion in NYHA functional class I, II, III, IV | 0.4, 0.3, 0.2, 0.1 | Assumption |
| Systolic blood pressure (mmHg) | 129 | CPRD |
| Total cholesterol (mg/dL) | 169 |
| Haemoglobin (g/dL) | 13.9 |
| Lymphocytes (%) | 26 | SHFM |
| Sodium (mEq/L) | 139 |
| Uric acid (mg/dL) | 8.9 |
| Proportion beta blocker use | 0.45 | CPRD |
| Proportion allopurinol use | 0.1 | SHFM |
| Proportion K+-sparing diuretic use | 0.03 |
| Diuretic dose (mg/kg) | 1.45 |
| Proportion ICD use  | 0 |
| Proportion CRT-D use  | 0 |
| *CPRD: Clinical Practice Research Datalink; CRT-D: cardiac resynchronization therapy defibrillator; ICD: implantable cardioverter-defibrillator; NYHA: New York Heart Association; SHFM: Seattle Heart Failure Model* |

## Event rates estimated from the model

To aid interpretation of the relationship between key patient characteristics and modelled event rates, the cumulative number of mortality and hospitalization events estimated by the model are presented in Figure S1, according to heart failure severity (defined according to New York Heart Association (NYHA) class), renin-angiotensin-aldosterone system inhibitor (RAASi) use and serum potassium status (normokalaemia or hyperkalaemia).

All settings were as described in the base case scenario with RAASi use, unless otherwise specified. NYHA class was held constant. In the normokalaemia scenario potassium levels of 4.5 mEq/L were modelled; while in the hyperkalemia scenario potassium levels were sampled around this point using a standard deviation of 0.5.mEq/L to allow the incidence of hyperkalemia events.

Figure S1. Model-estimated cumulative events over five years, according to NYHA class (a and c), RAASi use (b and d) and incidence of hyperkalemia (e)



*NYHA: New York Heart Association; RAASi: renin-angiotensin-aldosterone system inhibitor*

## References

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