**Online Appendix**

|  |  |
| --- | --- |
| CKD-EPI creatinine equation (28): | eGFR [mL/min/1.73 m²] = 141 x min(serum creatinine [mg/dL]/κ, 1)α x max(serum creatinine [mg/dL]/κ, 1)-1.209 x 0.993age [years] x 1.018 [if female] x 1.159 [if Black]  κ = 0.7 (females) or 0.9 (males)  α = -0.329 (females) or -0.411 (males) |
| CKD-EPI cystatin C equation (17): | eGFR [mL/min/1.73 m²] = 133 x min (cystatin C [mg/L]/0.8, 1)-0.499 x max (cystatin C [mg/L]/0.8, 1)-1.328 x 0.996Age [years] x 0.932 [if female] |
| CKD-EPI creatinine-cystatin C equation (17): | eGFR [mL/min/1.73 m²] = 135 × min (serum creatinine [mg/dL]/κ, 1)α ×  max(serum creatinine [mg/dL]/κ, 1)-0.601 × min(cystatin C [mg/L]/0.8, 1)-0.375 × max(cystatin C [mg/L]/0.8, 1)-0.711 × 0.995Age [years] × 0.969 [if female] × 1.08 [if black]  κ = 0.7 (females) or 0.9 (males)  α = -0.248 (females) or -0.207 (males) |
| sMDRD equation (18) | eGFR [mL/min/1.73 m²] = 175 × (serum creatinine [mg/dL])−1.154 × (age [years])−0.203 × 0.742 [if female] × 1.212 [if black] |
| keGFR equation (19)\* |  |

**Online Table 1:** Equations for GFR estimation

\*Variables entered into the keGFR equation included the baseline steady-state SCr (*SSPcr*) and the corresponding creatinine clearance (*CrCl,* calculated according to eGFR CKD-EPISCr), the mean and difference of current and previous SCr (*MeanPCr* and and the time between previous and current SCr . The maximum increase in creatinine per day if anuric () was assumed to bear a fixed value of 1.5 mg/dL.

**Online Table 2:** Adverse Events Considered Possibly, Probably, or Surely Related to the VFI Compound

|  |  |  |  |
| --- | --- | --- | --- |
| **Treatment emergent Adverse Events related to VFI** | | | |
| **Adverse Event** | **Number of Events** | **Relationship to VFI** | **Percentage of Patients (n=50)** |
| Diarrhea | 4 (3 mild, 1 moderate) | Possibly Related | 8% |
| Hypersensitivity to VFI | 2 (moderate) | Surely Related | 4% |
| Elevated Bilirubin | 2 (mild) | Possibly Related | 4% |
| Elevated CPK | 1 (mild) | Possibly Related | 2% |
| Elevated Aspartate Aminotransferase | 1 (mild) | Possibly Related | 2% |
| Pruritus | 1 (mild) | Possibly Related | 2% |
| Elevated Gamma-Glutamyl transferase | 1 (mild) | Possibly Related | 2% |
| Vertigo | 1 (mild) | Probably Related | 2% |

In 10/50 patients (20%) 13 related TEAEs were reported, 2 patients were discontinued due to hypersensitivity to VFI (urticaria and pruritus).

**Online Table 3:** mGFR, endogenous filtration markers and estimates of GFR

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | All patients  (Day 1) |  | Patients with two GFR measurements 48 hours apart  (Day 1) |  | Patients with two GFR measurements 48 hours apart  (Day 3) |  |
| n | 50 | ***p*** | 38 | ***p*** | 38 | ***p*** |
| mGFR (ml per min per 1.73m2) | 35 ±11.7 |  | 34.5 ±11.5 |  | 31.8 ±12.1 |  |
| eGFR sMDRD(ml per min per 1.73m2) | 40.4 ±17.1 | **0.0005** | 40.0 ±16.8 | **0.002** | 40.9 ±19.0 | **<0.0001** |
| eGFR CKD-EPISCr (ml per min per 1.73m2) | 40.4 ±18.5 | **0.001** | 40.1 ±18.2 | **0.005** | 40.9 ±20.3 | **<0.0001** |
| eGFR CKD-EPICysC (ml per min per 1.73m2) | 31 ±16.6 | **0.006** | 30.9 ±16.2 | **0.043** | 29.6 ±15.1 | 0.116 |
| eGFR CKD-EPISCr-CysC (ml per min per 1.73m2) | 34.6 ±17 | 0.747 | 34.4 ±16.7 | 0.944 | 34.0 ±17.2 | 0.161 |
| keGFR (ml per min per 1.73m2) | 41.4 ±18 | **0.0002** | 41.1 ±17.7 | **0.001** | 41.6 ±20.1 | **<0.0001** |

Data present GFR values at enrollment (day 1) and two days later (day 3). GFR data are presented as mean ± standard deviation. p shows p-value of comparison between mGFR and each GFR equation for each patient group (paired sample t-test). GFR data are rounded to one decimal place. mGFR is adjusted to body surface area according to Mosteller (26)

**Online Table 4:** Performance of SCr- and CysC-based equations when compared with measured GFR in AHF patients at day 3

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Mean ±SD | Mean bias ±SD | Pearson’s r | Precision | Accuracy | |
|  |  |  | **r** | **r2** | **P15** | **P30** |
| sMDRD | 40.9±19.0 | 9 ±10.1 | 0.88 | 0.78 | 29% | 66% |
| CKD-EPI SCr | 40.9±20.3 | 9 ±11.6 | 0.87 | 0.75 | 26% | 63% |
| CKD-EPI Cys | 29.6±15.1 | -2.2 ±8.8 | 0.81 | 0.66 | 26% | 61% |
| CKD-EPI Scr Cys | 34.0 ±17.2 | 2.1 ±9.1 | 0.86 | 0.75 | 34% | 71% |
| keGFR | 41.6±20.1 | 9.7 ±11.4 | 0.86 | 0.75 | 21% | 61% |

Accuracy P15 and P30 refers to percent of GFR estimates that are within 15% and 30% of measured GFR respectively.

SD = standard deviation, mean ±SD and mean bias ±SD are presented

**Online Figure 1:** Scatterplots of distribution and cumulative proportions of eGFR and mGFR at enrollment (day 1)



**A** Scatterplots of distribution of estimates of GFR and measured GFR at enrollment (day 1). Horizontal lines indicate means. **B** Cumulative Proportions of mGFR and formula-based estimates at enrollment (day 1). n=50

**Online Figure 2:** Scatterplots of distribution and cumulative proportions of eGFR and mGFR on day 3

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**A** Scatterplots of the distribution of estimates of GFR and measured GFR on day 3. Horizontal lines indicate means. **B** Cumulative Proportions of mGFR and formula-based estimates at day 3. n=38

**Online Figure 3:** Agreement between estimates of GFR versus measured GFR at enrollment (day 1)

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“Difference” indicates difference between estimated and measured GFR. “Average” shows average of eGFR and mGFR, **(A)** sMDRD, **(B)** CKD EPIScr,**(C)** CKD EPICys, **(D)** CKD EPIScr Cys, **(E)** keGFR. Solid line shows bias. Dotted lines show zero and bias ± 1.96 standard deviation. Data are presented in ml per min per 1.73m2. n=50

**Online Figure 4:** Correlation of percentage 48h changes of eGFR with corresponding percentage 48h changes of mGFR.



Percentage 48h change of eGFR according to sMDRD **(A)**, CKD EPISCr **(B)**, CKD EPICys **(C)** and CKD EPISCr-Cys **(D)**, keGFR **(E)** with changes of mGFR. Data are presented as percentage difference between day 1 and day 3, n=38. Arrows mark decreasing and increasing mGFR. Statistically significant, but weak positive correlations were observed between percentage 48h change of mGFR and eGFR sMDRD (Pearson’s r=0.36, p=0.044), eGFR CKD EPISCr (r=0.38, p=0.038), eGFR CKD EPISCr-Cys C (r=0.37, p=0.019), eGFR CKD EPICysC (r=0.35 p=0.02) and keGFR (r=0.39, p=0.016), respectively.

**Online Figure 5:** Correlation of percentage 48h changes of SCr (A) and of CysC (B) with corresponding 48h changes of mGFR.



Data are presented as percentage differences between day 1 and day 3, respectively. n=38. Arrows mark decreasing and increasing mGFR, respectively. A statistically significant, but weak negative correlation was observed between 48h changes in CysC and corresponding 48h changes of mGFR (r=-0.37, p=0.022), SCr changes did not correlate significantly (r=-0.31, p=0.057)

**AKI diagnosis based on CKD EPISCr back calculated serum creatinine**

mGFR corresponding back calculated hypothetical SCr changes were used to apply KDIGO AKI SCr criterion for AKI definition. Therefore the mGFR of study day 1 and 3 were put as resulting eGFR into CKD EPISCr equation and the formula was converted to put out the corresponding hypothetical SCr values for day 1 and 3. Did changes of back calculated SCr between day 1 and 3 reach or exceed 0.3mg/dl, mGFR based AKI was diagnosed according to KDIGO.

Example for caucasian male patient, age 82 years:

eGFR CKD EPISCr =

mGFRday 1: 23.8ml/min/1.73m2

mGFRday 3: 15.5 ml/min/1.73m2

back calculated SCrday 1 = = 2.43mg/dl

back calculated SCrday 3 = = 3.47mg/dl

The rise of back calculated SCr between day 1 and 3 of the example patient amounts 3.47-2.43mg/dl = 1.04mg/dl, so this patient would be diagnosed with mGFR based back calculated AKI.