Monitoring of Renal Function in Heart Failure

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University Medical Center Groningen
The Netherlands
Disclosures

- AAV received consultancy fees and/or research grants from: Alere, Bayer, Cardio3Biosciences, Celladon, Ceva, European Committee, Dutch Heart Foundation, Novartis, Servier, Torrent, Vifor.
Why should we monitor renal function in heart failure?

• Because they tell us about the prognosis of the patients?
• Because they might tell us about the hemodynamic status of the patient?
• Because they may influence/target therapy?
Predictive value of renal function in CHF

GFR\(_c\), baseline glomerular filtration rate; LVEF, left ventricular ejection fraction.

## CKD Meta-analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CKD Events</th>
<th>Total</th>
<th>no CKD Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madsen</td>
<td>22</td>
<td>38</td>
<td>27</td>
<td>38</td>
<td>1.3%</td>
<td>2.84 [1.43, 5.71] 1994</td>
<td></td>
</tr>
<tr>
<td>Hillege (PRIME II)</td>
<td>56</td>
<td>93</td>
<td>46</td>
<td>93</td>
<td>2.7%</td>
<td>2.38 [1.90, 2.98] 2000</td>
<td></td>
</tr>
<tr>
<td>Dries (SOLVD Treatment)</td>
<td>93</td>
<td>291</td>
<td>397</td>
<td>291</td>
<td>2.9%</td>
<td>2.22 [1.85, 2.66] 2000</td>
<td></td>
</tr>
<tr>
<td>Dries (SOLVD Prevention)</td>
<td>214</td>
<td>291</td>
<td>397</td>
<td>291</td>
<td>2.8%</td>
<td>1.80 [1.47, 2.20] 2000</td>
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<tr>
<td>Marenard</td>
<td>34</td>
<td>56</td>
<td>33</td>
<td>56</td>
<td>1.3%</td>
<td>2.76 [1.39, 5.48] 2001</td>
<td></td>
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<tr>
<td>McLellan</td>
<td>113</td>
<td>413</td>
<td>130</td>
<td>413</td>
<td>2.4%</td>
<td>1.77 [1.28, 2.45] 2002</td>
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<tr>
<td>Puligiano (IN-CHF)</td>
<td>16</td>
<td>202</td>
<td>168</td>
<td>202</td>
<td>1.5%</td>
<td>2.36 [1.28, 4.41] 2002</td>
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<tr>
<td>Muntwyler</td>
<td>34</td>
<td>293</td>
<td>33</td>
<td>293</td>
<td>1.7%</td>
<td>3.08 [1.81, 5.27] 2002</td>
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<tr>
<td>Ezekowitz (APPROACH)</td>
<td>438</td>
<td>3914</td>
<td>196</td>
<td>3914</td>
<td>2.9%</td>
<td>4.00 [3.36, 4.78] 2004</td>
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<tr>
<td>Akhter (VOMAC)</td>
<td>80</td>
<td>215</td>
<td>33</td>
<td>215</td>
<td>1.9%</td>
<td>4.18 [2.65, 6.61] 2004</td>
<td></td>
</tr>
<tr>
<td>MCKister</td>
<td>207</td>
<td>103</td>
<td>335</td>
<td>103</td>
<td>2.5%</td>
<td>2.20 [1.63, 2.97] 2004</td>
<td></td>
</tr>
<tr>
<td>Shlupak (DIG)</td>
<td>1309</td>
<td>3643</td>
<td>1066</td>
<td>3643</td>
<td>3.1%</td>
<td>1.71 [1.55, 1.89] 2004</td>
<td></td>
</tr>
<tr>
<td>Bollino-Domingo (HERS)</td>
<td>159</td>
<td>69</td>
<td>297</td>
<td>69</td>
<td>2.4%</td>
<td>1.98 [1.42, 2.76] 2004</td>
<td></td>
</tr>
<tr>
<td>Fonarow (ACHIERE)</td>
<td>1212</td>
<td>45990</td>
<td>1377</td>
<td>45990</td>
<td>3.1%</td>
<td>3.36 [2.10, 5.83] 2005</td>
<td></td>
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<tr>
<td>Smith (NHCP)</td>
<td>8948</td>
<td>36433</td>
<td>11869</td>
<td>36433</td>
<td>3.1%</td>
<td>2.24 [1.26, 3.93] 2005</td>
<td></td>
</tr>
<tr>
<td>Shlupak (CHS)</td>
<td>107</td>
<td>139</td>
<td>75</td>
<td>139</td>
<td>1.7%</td>
<td>2.77 [1.96, 4.62] 2005</td>
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</tr>
<tr>
<td>Go (ANCHOR)</td>
<td>16731</td>
<td>25902</td>
<td>7170</td>
<td>25902</td>
<td>3.1%</td>
<td>3.49 [2.36, 5.31] 2006</td>
<td></td>
</tr>
<tr>
<td>Hillege (CHARM)</td>
<td>320</td>
<td>1714</td>
<td>195</td>
<td>1714</td>
<td>2.8%</td>
<td>4.04 [2.31, 6.94] 2006</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th>CKD Events</th>
<th>Total</th>
<th>no CKD Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>98461</td>
<td>155440</td>
<td>100.0%</td>
<td>2.47</td>
<td>[2.23, 2.73]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total events:** 35377 26567

**Heterogeneity:** Tau² = 0.09; Chi² = 619.73, df = 45 (P < 0.00001); I² = 93%

**Test for overall effect:** Z = 17.43 (P < 0.00001)
### CKD Meta-analysis

<table>
<thead>
<tr>
<th>Model</th>
<th>HR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted CKD</td>
<td>2.47 (2.23 – 2.73)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Adjusted CKD</td>
<td>1.59 (1.49 - 1.69)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Adjusted severe CKD</td>
<td>2.17 (1.95 – 2.40)</td>
<td>P &lt; 0.001</td>
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</table>

No evidence of publication bias

Damman et al. 2012: paper submitted
## WRF in AHF: Meta-analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>WRF Events</th>
<th>WRF Total</th>
<th>no WRF Events</th>
<th>no WRF Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krumholz</td>
<td>119</td>
<td>469</td>
<td>235</td>
<td>1212</td>
<td>7.1%</td>
<td>1.41 [1.10, 1.82]</td>
<td>2000</td>
</tr>
<tr>
<td>Smith</td>
<td>35</td>
<td>185</td>
<td>27</td>
<td>227</td>
<td>5.0%</td>
<td>1.73 [1.00, 2.98]</td>
<td>2003</td>
</tr>
<tr>
<td>Forman</td>
<td>19</td>
<td>273</td>
<td>7</td>
<td>731</td>
<td>3.1%</td>
<td>7.74 [3.21, 18.62]</td>
<td>2004</td>
</tr>
<tr>
<td>Akhter</td>
<td>45</td>
<td>119</td>
<td>68</td>
<td>361</td>
<td>5.6%</td>
<td>2.62 [1.66, 4.13]</td>
<td>2004</td>
</tr>
<tr>
<td>De Silva</td>
<td>44</td>
<td>161</td>
<td>219</td>
<td>1055</td>
<td>6.2%</td>
<td>1.44 [0.98, 2.09]</td>
<td>2005</td>
</tr>
<tr>
<td>Jose</td>
<td>58</td>
<td>223</td>
<td>316</td>
<td>1631</td>
<td>6.6%</td>
<td>1.46 [1.06, 2.02]</td>
<td>2006</td>
</tr>
<tr>
<td>Khan</td>
<td>628</td>
<td>2060</td>
<td>879</td>
<td>4475</td>
<td>7.8%</td>
<td>1.79 [1.59, 2.02]</td>
<td>2006</td>
</tr>
<tr>
<td>Cowie</td>
<td>26</td>
<td>98</td>
<td>35</td>
<td>201</td>
<td>4.8%</td>
<td>1.71 [0.96, 3.05]</td>
<td>2006</td>
</tr>
<tr>
<td>Owam</td>
<td>1095</td>
<td>1419</td>
<td>3215</td>
<td>4633</td>
<td>7.7%</td>
<td>1.49 [1.30, 1.71]</td>
<td>2006</td>
</tr>
<tr>
<td>Cioffi</td>
<td>11</td>
<td>16</td>
<td>12</td>
<td>63</td>
<td>2.0%</td>
<td>9.35 [2.73, 31.99]</td>
<td>2007</td>
</tr>
<tr>
<td>Chittineni</td>
<td>10</td>
<td>107</td>
<td>17</td>
<td>402</td>
<td>3.4%</td>
<td>2.33 [1.04, 5.26]</td>
<td>2007</td>
</tr>
<tr>
<td>Iglesias</td>
<td>47</td>
<td>221</td>
<td>49</td>
<td>461</td>
<td>5.8%</td>
<td>2.27 [1.47, 3.52]</td>
<td>2008</td>
</tr>
<tr>
<td>Hata</td>
<td>29</td>
<td>275</td>
<td>1</td>
<td>101</td>
<td>0.9%</td>
<td>11.79 [1.58, 87.72]</td>
<td>2010</td>
</tr>
<tr>
<td>Kociol</td>
<td>1261</td>
<td>3581</td>
<td>5601</td>
<td>16482</td>
<td>7.9%</td>
<td>1.06 [0.98, 1.14]</td>
<td>2010</td>
</tr>
<tr>
<td>Lassus</td>
<td>18</td>
<td>46</td>
<td>67</td>
<td>246</td>
<td>4.3%</td>
<td>1.72 [0.89, 3.31]</td>
<td>2010</td>
</tr>
<tr>
<td>Herout</td>
<td>25</td>
<td>252</td>
<td>16</td>
<td>515</td>
<td>4.3%</td>
<td>3.43 [1.80, 6.56]</td>
<td>2010</td>
</tr>
<tr>
<td>Damman</td>
<td>30</td>
<td>106</td>
<td>76</td>
<td>894</td>
<td>5.4%</td>
<td>4.25 [2.62, 6.89]</td>
<td>2010</td>
</tr>
<tr>
<td>Belziti</td>
<td>12</td>
<td>46</td>
<td>25</td>
<td>154</td>
<td>3.5%</td>
<td>1.82 [0.83, 3.99]</td>
<td>2010</td>
</tr>
<tr>
<td>Breidhardt</td>
<td>49</td>
<td>136</td>
<td>171</td>
<td>521</td>
<td>6.1%</td>
<td>1.15 [0.78, 1.71]</td>
<td>2011</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>9861</td>
<td>34522</td>
<td>100.0%</td>
<td></td>
<td>1.99</td>
<td>[1.63, 2.42]</td>
<td></td>
</tr>
</tbody>
</table>

- Total events: 3572
- Heterogeneity: $\tau^2 = 0.13$; $\chi^2 = 146.49$, df = 19 ($P < 0.00001$); $I^2 = 87%$
- Test for overall effect: $Z = 6.81$ ($P < 0.00001$)
WRF Meta-analysis

Acute Heart Failure; Adjusted HR: 1.99 (1.43 - 2.71), P < 0.001

Evidence of Publication bias:

Damman et al. 2012: paper submitted
Potential Effects of Aggressive Decongestion During the Treatment of Decompensated Heart Failure on Renal Function and Survival

Jeffrey M. Testani, MD; Jennifer Chen, BS; Brian D. McCauley, BS; Stephen E. Kimmel, MD, MSCE; Richard P. Shannon, MD

Figure 1. Admission-to-discharge percentage change in GFR grouped by presence or absence of hemococoncentration. Hemoconcentration was defined as ≥2 of 3 of δ total protein, δ albumin, or δ hematocrit in the highest tertile.
Is Worsening Renal Function an Ominous Prognostic Sign in Patients With Acute Heart Failure? : The Role of Congestion and Its Interaction With Renal Function

Marco Metra, Beth Davison, Luca Bettari, Hengrui Sun, Christopher Edwards, Valentina Lazzarini, Barbara Piovanelli, Valentina Carubelli, Silvia Bugatti, Carlo Lombardi, Gad Cotter and Livio Dei Cas
Why should we monitor renal function in heart failure?

• Because they tell us about the prognosis of the patients?
• Because they might tell us about the hemodynamic status of the patient?
• Because they may influence/target therapy?
Autoregulation of the kidney

Intraglomerular Pressure

High

Low

Mean Arterial Pressure (mm Hg)

Normal

Chronic hypertension with chronic renal disease

Chronic hypertension with normal renal function

Autoregulation of the kidney

- Afferent arteriole
- Efferent arteriole
- Intra Glomerular pressure
Pathophysiology: renal blood flow

When Cardiac Index is reduced by 25%; RBF is decreased by 40%
Reduced renal blood flow (RBF): the main determinant of ↓ GFR in CHF

WITH ACE-inhibitor

Smilde et al. Clin Res Cardiol 2009
Monitoring Renal Function

Renal blood flow and Central Venous Pressure

GFR (ml/min/1.73m$^2$)

High RAP
Low RBF
Low RAP
Low RBF
High RAP
High RBF
Low RAP
High RBF

* $p<0.001$ for difference with High RAP, Low RBF.
† $p<0.01$ for difference with Low RAP, Low RBF.

Damman et al. Eur J Heart Fail 2007
Renal function and Central Venous Pressure

N=2738

- CI < 2.5 L/min/m²
- CI 2.5 - 3.2 L/min/m²
- CI > 3.2 L/min/m²

Damman et al. JACC 2009
Renal blood flow (RBF) and central venous pressure are main determinants of reduced GFR in CHF: Implications

1. Increase in cardiac output will increase RBF and therefore improve renal function
2. Decongestion will further improve renal function
Increase in Renal Tubular Damage after stopping diuretics in CHF

A

Furosemide stopped

KIM-1 (ng/gCr)

NAG (U/gCr)

Day 1, baseline
Day 1, 4 hours
Day 1, 8 hours
Day 2
Day 3
Day 4

*

†

Damman et al. JACC 2011
Improvement in renal function in CHF patients after decongestion

A

Furosemide 50 mg i.v.

Normal oral furosemide dose

KIM-1 (ng/gCr)

NAG (U/gCr)

Day 4, 0 hours
Day 4, 4 hours
Day 4, 8 hours
Day 7

Damman et al. JACC 2011
Dual effects of diuretics on renal function

- Loop diuretics might impair renal function by decreasing circulating volume and thereby reducing RBF
- Loop diuretics might impair renal function by activating the tubuloglomerular feedback
- But… Loop diuretics might improve renal function by decongestion
Why should we monitor renal function in heart failure?

- Because they tell us about the prognosis of the patients?
- Because they might tell us about the hemodynamic status of the patient?
- Because they may influence/target therapy?
Adenosine-A1 antagonist mechanism of action

1. Inhibits sodium reabsorption in the proximal tubule → enhances diuresis

2. Blocks adenosine-mediated vasoconstriction of afferent arteriole → maintains Glomerular Filtration Rate (GFR).
Adenosine-A1 antagonist

BG-9719 improves GFR and/or normalises diuretic mediated decline in GFR

Rolofylline, an Adenosine $A_1$–Receptor Antagonist, in Acute Heart Failure

Barry M. Massie, M.D., Christopher M. O’Connor, M.D., Marco Metra, M.D.,
Piotr Ponikowski, M.D., John R. Teerlink, M.D., Gad Cotter, M.D.,
Beth Davison Weatherley, Ph.D., John G.F. Cleland, M.D., Michael M. Givertz, M.D.,
Adriaan Voors, M.D., Paul DeLucca, Ph.D., George A. Mansoor, M.D.,
Christina M. Salerno, M.S., Daniel M. Bloomfield, M.D., and Howard C. Dittrich, M.D.,
for the PROTECT Investigators and Committees*
Primary Endpoint

Odds ratio (95% CI) vs Pbo: 0.92 (0.78, 1.09)

- Placebo: 36.0%
  - Treatment Success: 44.2%
  - Patient Unchanged: 19.8%
  - Treatment Failure: 21.8%
- Ro 30 mg: 40.6%
  - Treatment Success: 37.5%
  - Patient Unchanged: 21.8%
  - Treatment Failure: 21.8%

p=0.348 for comparison of distribution using the van Elteren extension of Wilcoxon test

Massie et al. NEJM 2010
Monitoring Renal Function

**Time to Death or CV/Renal Rehosp - Day 60**

Hazard Ratio (95% CI) = 0.98 (0.83, 1.17)

P-value = 0.861

**Study Day**

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Placebo (N=677)</th>
<th>Rolofylline 30 mg (N=1356)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>657</td>
<td>1322</td>
</tr>
<tr>
<td>14</td>
<td>633</td>
<td>1263</td>
</tr>
<tr>
<td>30</td>
<td>566</td>
<td>1134</td>
</tr>
<tr>
<td>55</td>
<td>489</td>
<td>1001</td>
</tr>
<tr>
<td>65</td>
<td>74</td>
<td>158</td>
</tr>
</tbody>
</table>

No. of patients at risk

Death: Placebo 9.5% vs rolofylline 8.9%

Re-hospitalization: Placebo 25.6% vs rolofylline 25.7%

Massie et al. NEJM 2010
Rolofylline did not improve renal function in PROTECT
Why should we monitor renal function in heart failure?

- Poor renal function and (maybe) WRF identify patients at higher risk
- Renal function can be used as the “hemodynamic eye”, since changes are related to cardiac output and venous congestion
Why should we monitor renal function in heart failure?

- Worsening renal function will influence therapy (diuretics/RAAS inhibitors)
- So far, no evidence that improvement of renal function per se will improve outcome in heart failure.