Chapter 6

Both in and outhospital worsening of renal function predict outcome in patients with heart failure

Results from the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH)

Kevin Damman, Tiny Jaarsma, Adriaan A. Voors, Gerjan Navis, Hans L. Hillege and Dirk J. van Veldhuisen
Abstract

Background

Impaired renal function and in-hospital worsening of renal function (WRF) are common in patients with heart failure and associated with poor outcome. The effect of WRF after discharge on outcome in these patients is unknown.

Methods and results

The Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH) included 1023 heart failure patients. We assessed estimated glomerular filtration rate (eGFR) and serum creatinine at admission, discharge, and 6 and 12 months after discharge. WRF was defined as increase in serum creatinine of > 0.3 mg/dL and >25%. The primary outcome was a composite of all-cause mortality and heart failure admissions. Mean age was 71 ± 11 years, 62% were male. Mean eGFR at admission was 55 ± 21 mL/min/1.73m² while mean LVEF was 33 ± 14%. In-hospital WRF occurred in 11% of patients, while 16% and 9% experienced WRF from 0 to 6, and 6 to 12 months after discharge, respectively. The occurrence of WRF or lower eGFR over time was associated with lower baseline eGFR, anemia, history of hypertension, type II diabetes, peripheral artery disease, and higher age. In multivariate analysis, WRF at any point in time was associated with worse prognosis: HR 1.41 (1.01–1.97), P = 0.047 for in-hospital WRF, HR 1.94 (1.13 – 3.34), P = 0.016 for WRF between 0-6 months, and HR 3.47 (1.36 – 8.87), P = 0.009 for WRF between 6-12 months.

Conclusion

Both in and out-of-hospital worsening of renal function are independently related to poor prognosis in patients with heart failure, suggesting that renal function in heart failure patients should be monitored long after discharge.
Introduction

Renal impairment is common in both patients with acute heart failure (AHF), and patients with chronic heart failure (CHF). In both patient groups, renal impairment is a prominent predictor of poor survival and (re)hospitalizations for heart failure [1-4]. However, not only baseline renal function is important in these patients, but also worsening renal function (WRF) is an independent predictor of prognosis [5-7]. In a pooled analysis of 8 studies, we recently showed that WRF was associated with a significantly higher mortality rate in both patients with AHF and CHF [8]. Results of the AHF studies were based on WRF which was defined as inhospital worsening of renal function [6,7,9-14]. Importantly, WRF is also frequently observed after discharge in both patients with heart failure and after myocardial infarction, but to this date there is no information of the effect of such worsening of renal function on prognosis [5,15-17]. While outhospital WRF is an important predictor of prognosis in patients with stable CHF [5,15], it is important to know whether similar associations are present in patients with AHF, long after they have been discharged from the hospital. In the present study, we therefore set out to investigate the effect of WRF at different time points during hospitalization and after discharge on prognosis in AHF patients who participated in the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH) [18].

Methods

This was a retrospective analysis of the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH), a multicenter, randomized, open trial, with blinded endpoint evaluation, designed to compare basic support and intensive support in patients with heart failure, after hospitalization for AHF, which was conducted from 2002 to 2007 in The Netherlands. A detailed description of the rationale, design, and results of the COACH has been previously published [18,19]. Patients with both reduced and preserved left ventricular ejection fraction (LVEF) were allowed to participate in the study. Patients were routinely followed every 6 months after discharge in all treatment groups, and additional visits in the intensive support and moderate support groups. For comparison purposes, only the 6 months visits, which were available in all treatments arms were used for the primary analysis.

Renal function and WRF

We estimated the glomerular filtration rate (eGFR) using the simplified Modification of Diet in Renal Disease formula (186.3 x (serum creatinine (mg/dL))^{-1.154} x age^{-0.203} x (0.742 if female) (mL/min/1.73m^2)), at admission, discharge, 6 months, 12 months and 18 months after discharge [20]. For patients without serum creatinine at discharge, the last known serum creatinine during hospitalization used. WRF was defined as an absolute increase in serum creatinine >0.3mg/dL in combination with >25% increase in serum creatinine between two time points, the latter chosen to adjust for the exponential relationship between eGFR and...
serum creatinine [6]. We evaluated WRF at the following time points: from admission to discharge, from discharge to 6 months follow up, and from 6 months to 12 months follow up. For determination of predictors of the occurrence of WRF, and slope of eGFR over time, also WRF from discharge to 2 months and WRF from 2 months to 6 months follow up were considered in patients that attended those visits according to protocol. Serum creatinine at admission was available in all patients, and a discharge serum creatinine was available in 98% (1000) of patients. Among survivors, 72% (647), 73% (582) and 75% (562) had a serum creatinine at 6, 12 and 18 months follow up, respectively.

Follow-up and prognosis

Patients were followed for 18 months after index hospitalization. The present analysis was conducted using the same endpoints as the main study. There were two primary endpoints of the COACH: a composite endpoint of heart failure hospitalization and all-cause mortality. A second primary endpoint was the number of ‘unfavourable days’. This is the number of days a patient is not alive or not out of hospital, as described earlier.[18,19] Secondary endpoints included the individual endpoints in the primary endpoint, all-cause hospitalizations and the number of all-cause hospitalizations per patient.

Statistical analysis

Data are given as mean ± standard deviation when normally distributed, as median and interquartile range when skewed distributed, and as frequencies and percentages for categorical variables. Associations between baseline variables were evaluated by means of 1-way ANOVA, the Kruskal-Wallis test, and χ² or Fisher exact tests, when appropriate. To establish continuous change of renal function over time, and the association with demographic variables, we used two types of analysis. First, we analyzed the occurrence of WRF (> 0.3 mg/dL and > 25% increase in serum creatinine) during the total follow up. Time to determination of serum creatinine was used as follow up variable. A Cox proportional hazard analysis, with WRF being the failure variable, was used to determine univariate and multivariate predictors of the occurrence of WRF. Second, we constructed a multilevel mixed-effects linear model using the xtmixed command in STATA to investigate the determinants of the slope of eGFR over time. Finally, we used a Cox proportional hazards model to estimate hazard ratios with 95% confidence intervals (CI) for the association between WRF and prognosis, and in a secondary model we estimated the effect of time-varying eGFR on outcome. Missing values were imputed using expectation maximization as estimation method. Two-sided P values were used, taking P < 0.05 to be statistically significant. Statistical analyses were performed using SPSS, Chicago version 12.0 and STATA, College Station, Texas, version 10.0.
Results

In the present analysis, all 1023 patients who were randomized in the COACH were included. Table 1 shows characteristics at baseline (admission) for the study population and the characteristics for the different subgroups of patients that experienced WRF. Mean age was 71 ± 11 years, while 62% were male. Mean eGFR was 55 ± 21 mL/min/1.73m², while 59% had chronic kidney disease as defined as eGFR below 60 mL/min/1.73m².

During index hospitalization, the mean change in serum creatinine showed a normal distribution, with a mean delta serum creatinine of 0.01 ± 0.44 mg/dL (Figure 1A). Changes in serum creatinine from discharge to 6 months, from 6 months to 12 months, and 12 to 18 months follow up were also normally distributed and showed a mean delta serum creatinine of 0.08 ± 0.45 mg/dL, 0.05 ± 0.34 mg/dL, and 0.04 ± 0.44 mg/dL, respectively (Figure 1B-D). This corresponded to a change in eGFR of -1.1 inhospital, and -2.1, -2.3, and -0.7 mL/min/1.73m², respectively per 6 month follow up.

Inhospital WRF occurred in 11% of patients, while 16% and 9% of patients experienced WRF from discharge to 6 months, and from 6 to 12 months follow-up, respectively. Of those
# Table 1. Baseline characteristics according to the occurrence of WRF

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No WRF (N = 763)</th>
<th>WRF Inhospital (N = 106)</th>
<th>WRF 0 – 6 months (N = 101)</th>
<th>WRF 6 – 12 months (N = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70 ± 12</td>
<td>73 ± 11*</td>
<td>73 ± 10*</td>
<td>71 ± 9</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>64</td>
<td>59</td>
<td>55</td>
<td>77</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>33 ± 14</td>
<td>36 ± 16</td>
<td>34 ± 14</td>
<td>34 ± 13</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>51</td>
<td>44</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>IV</td>
<td>44</td>
<td>49</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>118 ± 21</td>
<td>119 ± 21</td>
<td>118 ± 22</td>
<td>124 ± 23</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>68 ± 12</td>
<td>69 ± 12</td>
<td>69 ± 14</td>
<td>69 ± 12</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>75 ± 13</td>
<td>75 ± 13</td>
<td>74 ± 14</td>
<td>74 ± 14</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>42</td>
<td>45</td>
<td>52*</td>
<td>54</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>44</td>
<td>45</td>
<td>48</td>
<td>40</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26</td>
<td>30</td>
<td>38</td>
<td>28</td>
</tr>
<tr>
<td>Stroke</td>
<td>9</td>
<td>11</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>COPD</td>
<td>26</td>
<td>31</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>PAD</td>
<td>15</td>
<td>24</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>MI</td>
<td>43</td>
<td>34</td>
<td>52*</td>
<td>51</td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.41 ± 0.7</td>
<td>1.24 ± 0.4*</td>
<td>1.37 ± 0.6</td>
<td>1.39 ± 0.4</td>
</tr>
<tr>
<td>Blood urea nitrogen (mmol/L)</td>
<td>11 ± 6</td>
<td>10 ± 6</td>
<td>11 ± 5</td>
<td>11 ± 6</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>56 ± 22</td>
<td>60 ± 21</td>
<td>57 ± 22</td>
<td>56 ± 21</td>
</tr>
<tr>
<td>Hemoglobin levels (g/dL)</td>
<td>13.5 ± 2.0</td>
<td>13.5 ± 2.0</td>
<td>13.1 ± 1.8*</td>
<td>13.9 ± 1.9</td>
</tr>
<tr>
<td>Medication (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi</td>
<td>50</td>
<td>51</td>
<td>60</td>
<td>63</td>
</tr>
<tr>
<td>ARB</td>
<td>13</td>
<td>12</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>46</td>
<td>43</td>
<td>43</td>
<td>54</td>
</tr>
<tr>
<td>Loop Diuretics</td>
<td>75</td>
<td>75</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>Digoxin</td>
<td>22</td>
<td>21</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Statins</td>
<td>33</td>
<td>41</td>
<td>33</td>
<td>47</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>20</td>
<td>23</td>
<td>21</td>
<td>30</td>
</tr>
</tbody>
</table>

* P < 0.05 for difference with no WRF. Abbreviations: LVEF: left ventricular ejection fraction, NYHA: New York heart association, SBP: systolic blood pressure, DBP: diastolic blood pressure, COPD: chronic obstructive pulmonary disease, PAD: peripheral artery disease, MI: history of myocardial infarction, eGFR: estimated glomerular filtration rate, ACEi: angiotensin converting enzyme inhibition, ARB: angiotensin II receptor antagonist
patients who experienced WRF between discharge and 6 months, only 9% had experienced WRF in hospital. In contrast, 26% of patients that experienced WRF from 6 to 12 months follow-up had experienced WRF during hospitalization or from discharge to 6 months. During 18 months follow-up, mean eGFR among survivors decreased from 60 ± 24 mL/min/1.73 m² at admission to 53 ± 23 mL/min/1.73 m² after 18 months (Figure 2).

**Predictors of occurrence of WRF and change in eGFR over time**

After 18 months follow-up, in total 260 (25%) of patients had experienced WRF at any point in time. In univariate analysis, significant predictors of WRF were a history of type II diabetes (Hazard ratio (HR) 1.53, 95% confidence interval (CI) 1.14 to 2.03, \( P = 0.004 \)), peripheral artery disease (HR 1.44 (95% CI 1.06 to 1.94) \( P = 0.019 \)), age (HR 1.17 per 10 years increase (95% CI 1.05 to 1.31), \( P = 0.007 \)), as well as the presence of anemia (HR 1.42 (95% CI 1.11 to 1.84), \( P = 0.008 \)). Randomized treatment assignment showed no effect on the occurrence of WRF. Table 2 shows the outcome of the multivariate analysis, showing that age, type II diabetes, and anemia, were independent predictors of the occurrence of WRF.

![Figure 2. Change of mean eGFR over time in survivors. Abbreviations: eGFR: estimated glomerular filtration rate](image)
In a multilevel mixed-effects linear model estimating eGFR change over time, the most important predictor of eGFR change was renal function at admission. Other predictors included a history of hypertension, type II diabetes, atrial fibrillation, pulmonary disease, and
Peripheral artery disease, low sodium diet, gender, age, beta-blocker therapy and hemoglobin levels. The multivariate mixed model results are depicted in table 3. These results indicate that the slope of eGFR over time is particularly dependent on baseline eGFR, a fixed effect, with an extra random effect of baseline eGFR on the individual patient level.

**Prognosis.**

During the 18 months follow up of the study, in total 411 patients reached the primary endpoint. Both eGFR at admission (HR 1.23 per 10 mL/min/1.73 m² decrease, 95% CI 1.17 to 1.29, \( P < 0.001 \)), and eGFR at discharge (HR 1.24 per 10 mL/min/1.73 m² decrease, 95% CI 1.17 to 1.30, \( P < 0.001 \)), were prominent predictors of survival. Inhospital WRF was not a predictor of the primary endpoint on the long term HR 1.24, 95% CI 1.92 to 1.68, \( P = 0.157 \) (figure 3a). Both WRF from discharge to 6 months HR 1.62, 95% CI 1.08 to 2.43, \( P = 0.019 \) and WRF from 6 to 12 months HR 3.71, 95% CI 1.84 to 7.49, \( P < 0.001 \), were related to a poor outcome (Figure 3b and 3c). In a landmark analysis, WRF at any of the pre-specified time-intervals was significantly related to impaired prognosis (Figure 4). This resulted in a HR 1.55, 95% CI 1.07 to 2.26, \( P = 0.022 \), for inhospital WRF, HR 2.02, 95% CI 1.20 to 3.40, \( P = 0.008 \) for WRF between 0 and 6 months and HR 3.68, 95% CI 1.83 to 7.41, \( P < 0.001 \) for WRF between 6 and 12 months (all 6 months follow up). Table 4 shows the unadjusted and adjusted hazard ratio’s for WRF at the different time points for all endpoints with 6 months follow up for each category. WRF during any time was independently associated with a greater risk for the primary endpoint of all-cause mortality and heart failure hospitalizations. This was mainly attributable to the effect on all-cause mortality, with the effect on heart failure admissions subsiding in multivariate analysis.

In a secondary model, we investigated the relationship of eGFR with the primary endpoint when introduced as a time-dependent covariate. In multivariate analysis, eGFR was an independent predictor of the combined endpoint (HR 1.19 per 10 mL/min/1.73 m² decrease
Chapter 6

Other independent time dependent predictors were hemoglobin levels (HR 1.13 per g/dL decrease (95% CI 1.04 to 1.23), \( P = 0.005 \)), age (HR 1.03 per year increase (95% CI 1.01 to 1.06), \( P = 0.006 \)), and diuretic use (HR 2.64 (95% CI 1.05 to 6.63), \( P = 0.039 \)).

Table 4. Relationship between occurrence of WRF and outcome

<table>
<thead>
<tr>
<th>Events</th>
<th>WRF inhospital (N = 1000)</th>
<th>WRF from 0 to 6 months (N = 632)</th>
<th>WRF from 6 to 12 months (N = 476)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted HR (95% CI)</td>
<td>Adjusted* HR (95% CI)</td>
<td>Unadjusted HR (95% CI)</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>1.55 (1.07 – 2.26)†</td>
<td>1.63 (1.10 – 2.40)†</td>
<td>2.02 (1.20 – 3.40)‡</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.86 (1.17 – 2.94)‡</td>
<td>1.73 (1.16 – 2.60)‡</td>
<td>2.47 (1.29 – 4.74)‡</td>
</tr>
<tr>
<td>Heart failure hospitalizations</td>
<td>1.30 (0.78 – 2.17)</td>
<td>1.50 (0.89 – 2.53)</td>
<td>1.76 (0.95 – 3.27)</td>
</tr>
<tr>
<td>All-cause hospitalizations</td>
<td>1.47 (1.08 – 1.99)†</td>
<td>1.57 (1.15 – 2.15)‡</td>
<td>1.57 (0.90 – 2.75)</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, NYHA class, LVEF, treatment assignment, systolic and diastolic blood pressure, heart rate, hemoglobin levels, eGFR at baseline, the occurrence of WRF before the studied period, medical therapy, history of myocardial infarction / atrial fibrillation / diabetes / stroke / COPD / Hypertension / Peripheral artery disease / time since diagnosis of heart failure
† \( P < 0.05 \)
‡ \( P < 0.01 \)
# \( P < 0.001 \)

Figure 5 shows the association between the second primary endpoint of the COACH (unfavourable days) and the occurrence of WRF. In general, the presence of WRF resulted in a significantly higher number of unfavourable days compared to patients without WRF. Especially patients who experienced WRF after discharge showed a significantly higher number of unfavourable days compared to patients with preserved renal function.
Discussion

Our present study is the first to show that in patients with AHF not only WRF during hospitalization, but also WRF on short and moderate time span after hospitalization is common and associated with impaired survival. WRF after hospitalization is associated with a higher number of unfavourable days compared to patients that had relatively preserved renal function.

Renal impairment at any point in time has been recognized as an important risk factor in both CHF and AHF. When present, decreased renal function predisposes to further worsening of renal function [7,15]. In a recent meta-analysis, we showed that both in AHF and CHF patient populations, the risk associated with WRF for all-cause mortality was similar [8]. Furthermore, we showed that the risk associated with a decline in renal function started to rise when an increase in serum creatinine was observed of > 0.3 mg/dl. This cut-off for WRF has been used by others, and has been suggested as clinically meaningful [5,14]. To address the exponential relationship between serum creatinine, we included also a relative increase in serum creatinine in our definition of WRF, which may give a more reliable estimate of WRF. [7] Using this definition, the incidence of inhospital WRF in the COACH-study was 11%, which was slightly lower compared to other AHF studies, in which percentages of 12-55% have been observed, depending on definition. The outhospital incidence of WRF (16% and 9%), was more or less similar to the incidence observed in populations with CHF patients. Our sub

![Figure 4. Landmark analysis of the relationship between WRF and outcome. * P < 0.01, † P < 0.001. Reference group of No WRF depicts patients who did not have WRF during that particular time period. Patients who experience an endpoint in a previous period are excluded from subsequent analyses. Abbreviations: WRF: worsening renal function]
analysis of the COACH study is the first to investigate changes in renal function both during hospitalization and after discharge in the same patient with heart failure. Our results indicate that even long after discharge, these patients are at increased risk for WRF, and should be monitored closely.

**WRF and prognosis**

In agreement with other studies in both AHF and CHF, WRF in our population was a strong and independent predictor of the primary endpoint of the COACH trial, which consisted of heart failure (re)hospitalization and all-cause mortality. The relative risk observed with WRF increased with time after index hospitalization, with the highest mortality of re-hospitalization risk observed when WRF occurred between 6 and 12 months post-discharge. The increased risk with WRF was mainly attributable to an increased all-cause mortality risk. This is consistent with findings from our recent meta-analysis, showing only a borderline increase in the risk for heart failure hospitalization [8]. We also analyzed the relationship between WRF and unfavourable days, the second primary endpoint of the COACH study. WRF occurrence was associated with a significant increase in unfavourable days, especially when WRF was observed outhospital. This is the first analysis to show that WRF is not only associated with an increased risk for mortality, but to a higher number of unfavourable days as well.

**Pathophysiology of WRF**

The pathophysiology of renal impairment in heart failure is mainly attributable to decreased renal perfusion and venous congestion, while endothelial dysfunction, neurohormonal activation and inflammation play a mediating role [21,22]. The driving force behind WRF is much less established. In a recent study, Metra et al found that baseline renal impairment, reduced ejection fraction, NYHA class and diuretic dose were independent determinants of WRF [7]. Diuretic use and dosing have been established as important risk factors for WRF in

![Figure 5. Relationship between occurrence of WRF and unfavourable days in the COACH. * P < 0.05](image)
other studies [15,23]. Other factors established as risk factors for WRF include the presence of vascular disease, hemoglobin and blood pressure [5,15,24]. Our present analysis confirmed baseline renal impairment and reduced hemoglobin levels as prominent predictors of WRF or decreasing GFR. In addition, we were able to show in a longitudinal mixed effects multilevel model that the slope of eGFR was also dependent of baseline eGFR and anemia, but also age, low sodium diet on admission, hypertension, peripheral artery disease, and type II diabetes. To our knowledge, we are the first to use this kind of estimation models to predict determinants of the slope of renal function over time.

Our results, and those previously published, seem to indicate that WRF (or lower eGFR over time) is especially observed in those with many comorbidities. The association with diabetes may indicate the occurrence of diabetic nephropathy, while the association with peripheral artery disease may have a relationship with either renal artery stenosis, or general atherosclerosis [25,26]. Low sodium diet as a predictor of WRF may be a representation of treatment bias; especially volume overload patients (sicker patients) are likely to be advised to use a low sodium diet. Finally, the association between lower hemoglobin levels and anemia with lower eGFR may be bidirectional, while also reduced renal function may predispose to the occurrence of anemia [27].

Clinical implications

Our present analysis has some important clinical implications. First, our study confirms earlier reports that WRF is frequently observed in patients with heart failure, both in and out of hospital. Second, while WRF occurs also shortly after discharge, patients should be monitored closely in the weeks and months following admission: WRF at any time after discharge heralds a worse prognosis. Initiation of adequate therapy may prevent further WRF and eventually also improve renal function. Third, the effect of WRF on mortality and morbidity should be acknowledged. Although an increase in serum creatinine > 0.3 mg/dL may seem insignificant, it increases the risk for all cause mortality substantially. Finally, predisposing and modifiable factors to WRF should be monitored and possibly treated. These may include anemia, baseline renal impairment and diuretic use. Future studies are needed to assess whether treatment targeted at prevention or preservation of renal function will lead to improvement in mortality and morbidity.

Limitations

This is a retrospective analysis of a randomized controlled trial. We did not measure renal hemodynamics or GFR by clearance methods, and the used estimated GFR formula is only a surrogate marker of real GFR, but has been shown to be the most accurate in heart failure [20]. The definition used to determine WRF has been used by multiple previous studies, but the cut-off value of > 0.3 mg/dl increase in serum creatinine is arbitrary. We have shown in our recent meta-analysis that the relative risk for mortality rises steeply above >0.3mg/dl increase, and therefore this cut-off seems justifiable.
Conclusions

In our present retrospective analysis of the COACH, we found that WRF is not only prevalent in hospital, but also on short and moderate time span after hospitalization in patients with AHF. WRF was associated with impaired survival and morbidity especially when WRF occurred late after discharge.

Acknowledgements

The COACH study was supported by the Netherlands Heart Foundation (grant 2000Z003). K. Damman is supported by the Netherlands Heart Foundation (grant 2006B157) A.A. Voors and D.J. van Veldhuisen are Clinical Established Investigators of the Netherlands Heart Foundation (grants 2006T37 and D97-017, respectively).

Disclosures

None.
References


WRF at different timepoints and outcome