Prognostic Importance of Early Worsening Renal Function After Initiation of Angiotensin-Converting Enzyme Inhibitor Therapy in Patients With Cardiac Dysfunction

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Background—Worsening renal function (WRF) in the setting of heart failure has been associated with increased mortality. However, it is unclear if this decreased survival is a direct result of the reduction in glomerular filtration rate (GFR) or if the mechanism underlying the deterioration in GFR is driving prognosis. Given that WRF in the setting of angiotensin-converting enzyme inhibitor (ACE-I) initiation is likely mechanistically distinct from spontaneously occurring WRF, we investigated the relative early WRF-associated mortality rates in subjects randomized to ACE-I or placebo.

Methods and Results—Subjects in the Studies Of Left Ventricular Dysfunction (SOLVD) limited data set (n=6337) were studied. The interaction between early WRF (decrease in estimated GFR ≥20% at 14 days), randomization to enalapril, and mortality was the primary end point. In the overall population, early WRF was associated with increased mortality (adjusted hazard ratio [HR], 1.2; 95% CI, 1.0–1.4; P=0.037). When analysis was restricted to the placebo group, this association strengthened (adjusted HR, 1.4; 95% CI, 1.1–1.8; P=0.004). However, in the enalapril group, early WRF had no adverse prognostic significance (adjusted HR, 1.0; 95% CI, 0.8–1.3; P=1.0; P=0.09 for the interaction). In patients who continued to receive study drug despite early WRF, a survival advantage remained with enalapril therapy (adjusted HR, 0.66; 95% CI, 0.5–0.9; P=0.018).

Conclusions—These data support the notion that the mechanism underlying WRF is important in determining its prognostic significance. Specifically, early WRF in the setting of ACE-I initiation appears to represent a benign event that is not associated with a loss of benefit from continued ACE-I therapy. (Circ Heart Fail. 2011;4:685-691.)

Key Words: cardiorenal syndrome ■ worsening renal function ■ kidney ■ ACE inhibitor

Worsening renal function (WRF) has been associated with increased mortality in both inpatients and outpatients with cardiac failure.1–8 In most prior research in this area, WRF has been studied as a single entity, regardless of the inciting mechanism. This may not be unreasonable given that the reduction in glomerular filtration rate (GFR) itself has been proposed as a direct pathophysiological contributor to heart failure disease progression.9,10 However, recent data suggest that WRF may actually represent a heterogeneous group of disorders with different underlying mechanisms and potentially prognostic implications.11–13 Notably, some patients appear to be intrinsically susceptible to the development of WRF, a predisposition that occurs independently of treatment, such as aggressive diuresis.12 These observations raise the possibility that much of the risk associated with WRF is simply a reflection of underlying disease severity and that the reduction in GFR may be of secondary importance.

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The initiation of angiotensin-converting enzyme inhibitor (ACE-I) therapy causes alterations in intraglomerular hemo-
dynamics, potentially leading to a decrease in filtration fraction and a resultant reduction in GFR.14 As such, WRF has been reported at an increased frequency after initiation of these agents. Despite this early deterioration in renal function, the long-term renal outcomes may actually be superior in patients with early ACE-I–induced WRF, with WRF potentially acting as a marker of baseline renal physiology that stands to derive the most benefit from renin-angiotensin-al-dosterone system antagonism.15–17 However, the effect of ACE-I–induced WRF on mortality in the setting of heart failure has yet to be determined. The Studies Of Left Ventricular Dysfunction (SOLVD) trials18,19 were randomized placebo-controlled trials of enalapril in subjects with cardiac dysfunction. Given that assignment to enalapril or placebo was random, we hypothesized that if the reduction in GFR is directly causative of the reduced survival associated with early WRF, a similar early WRF-associated mortality would be expected in the placebo and enalapril groups. However, if the predominant driver for early WRF-associated mortality is advanced cardiorenal disease found in these patients, then early WRF in the enalapril group (which is
potentially treatment induced) should prognostically be of limited significance. As such, the primary objective of this study was to compare the relative prognostic importance of early WRF in patients randomized to enalapril compared with placebo in the SOLVD population.

**Methods**

The SOLVD prevention and treatment trials were National Heart, Lung, and Blood Institute (NHLBI)–sponsored, randomized, double-blind, placebo-controlled trials of the effect of enalapril in patients with asymptomatic and symptomatic left ventricular dysfunction and compose the overall SOLVD population. Methods and results have been previously published.18,19 Briefly, 4228 patients were enrolled in the prevention trial and 2569 were enrolled in the treatment trial at 23 international centers (N=6797). Inclusion in either trial required an ejection fraction ≤35% and an age between 21 and 80 years. Patients not receiving medication for the treatment of heart failure who demonstrated no evidence of heart failure at the end of a 3-week run-in period were eligible for the prevention trial. Eligibility for the treatment trial required a diagnosis of heart failure and the use of medications for this condition. Exclusion criteria included a baseline creatinine level >2.5 mg/dL, severe or unstable coronary or valvular disease, suspected renal artery stenosis, or any other disease that may shorten survival or impede participation in the long-term trial. Prior use of angiotensin inhibitor therapy was not a contraindication to enrollment.

The estimated GFR (eGFR) was calculated using the Modified Diet and Renal Disease equation.20 Early WRF was defined as a 20% decrease in eGFR from baseline to 14 days after randomization to study drug, the first postrandomization serum creatinine level.21 The entire SOLVD population was analyzed as a whole to maximize power, given the lack of interaction between trials (prevention vs treatment) and early WRF in the overall trial (P=0.38), the placebo group (P=0.42), or the enalapril group (P=0.62). The SOLVD trials were conducted and supported by the NHLBI in collaboration with the SOLVD study investigators. This analysis was conducted using a limited access data set obtained from the NHLBI and does not necessarily reflect the opinions or views of the SOLVD investigators or the NHLBI.

The primary analyses in this study focused on the risk for mortality associated with early WRF in patients randomized to placebo or enalapril. The primary end point was the interaction between early WRF, mortality, and study drug assignment. Values reported are mean±SD, median (quartile 1–4), and percentile. An independent Student t test or the Mann-Whitney U test was used to compare continuous parameters. The Pearson χ² test was used to evaluate categorical variables. Proportional hazards modeling was used to evaluate time-to-event associations with all-cause mortality. Candidate covariates for multivariable modeling were obtained by screening all baseline variables with a univariate association with mortality (ie, age, race, ejection fraction, heart rate, diastolic blood pressure, New York Heart Association class, serum sodium level, eGFR, history of diabetes mellitus, hypertension, stroke or myocardial infarction, loop diuretic, potassium-sparing diuretic, digoxin, β-blocker use, and randomization to enalapril) (HR, 1.2; 95% CI, 1.0–1.4; P=0.037) (goodness-of-model fit test P=0.48).

Of the 6377 patients in the current analysis, 49.8% were randomized to enalapril and 50.2% were randomized to placebo. The net deterioration in eGFR from baseline to 14 days after randomization was slightly greater in the enalapril group compared with placebo (-0.7±1.2 vs 0.4±1.5 mL/min per 1.73m²; P=0.002). Early WRF tended to occur more frequently in the enalapril group, but this difference did not meet statistical significance (odds ratio, 1.2; 95% CI, 0.99–1.4; P=0.06). In patients assigned to placebo, early WRF was significantly associated with increased mortality (HR, 1.3; 95% CI, 1.1–1.7; P=0.012). This relationship was strengthened by adjusting for baseline eGFR (HR, 1.7; 95% CI, 1.4–2.2; P<0.0001) and persisted after extensively adjusting for baseline characteristics associated with mortality (ie, age, race, ejection fraction, heart rate, diastolic blood pressure, New York Heart Association class, serum sodium level, eGFR, history of diabetes mellitus, hypertension, stroke or myocardial infarction, loop diuretic, potassium-sparing diuretic, digoxin, and β-blocker use) (HR, 1.4; 95% CI, 1.1–1.8; P=0.004) (goodness-of-model fit test P=0.34). However, in patients randomized to enalapril, early WRF was not associated with increased mortality (HR, 1.0; 95% CI, 0.78–1.3; P=1.0; P=0.09 for the interaction) (Figure 1). This lack of association persisted after adjustment for baseline eGFR (HR, 1.2; 95% CI, 0.94–1.5; P=0.15; P=0.04 for the interaction) and

**Results**

Baseline characteristics and the effect of randomization to enalapril on mortality in the SOLVD trials have been previously reported.16,19 In addition, the strong association between baseline renal dysfunction and reduced survival has been previously described in both asymptomatic and symptomatic patients in the SOLVD data set.22 Characteristics of the 6377 patients with data on renal function both at baseline and 14 days are presented in Table 1. In total, 606 patients (9.5%) experienced early WRF between baseline and 14 days after randomization, with a mean±SD decrease in eGFR of 29.2±9.8% in the enalapril group and 29.9±9.3% in the placebo group. Patients experiencing early WRF at 14 days had a significant recovery of renal function by 1 year (P<0.0001), and the degree of recovery was similar between those assigned to enalapril or placebo (16.0±34.1% vs 18.2±38.0%; P=0.52). Characteristics of patients with and without early WRF are presented in Table 1. Early WRF was not significantly associated with all-cause mortality in a univariate model (hazard ratio [HR], 1.2; 95% CI, 0.98–1.4; P=0.10). However, baseline eGFR was significantly higher in patients who ultimately developed early WRF (Table 1), potentially confounding this association. After adjustment for baseline eGFR, early WRF demonstrated a highly significant association with mortality (HR, 1.4; 95% CI, 1.2–1.7; P<0.0001). This association remained significant after extensive adjustment for baseline characteristics associated with mortality (ie, age, race, ejection fraction, heart rate, diastolic blood pressure, New York Heart Association class, serum sodium level, eGFR, history of diabetes mellitus, hypertension, stroke or myocardial infarction, loop diuretic, potassium-sparing diuretic, digoxin, β-blocker use, and randomization to enalapril) (HR, 1.2; 95% CI, 1.0–1.4; P=0.037) (goodness-of-model fit test P=0.48).
baseline characteristics associated with mortality (HR, 1.0; 95% CI, 0.78–1.3; P = 0.09 for the interaction). The goodness-of-fit test value was P = 0.26 for the model in the strata of patients randomized to enalapril and P = 0.28 for the full interaction model. An analysis of alternative definitions of early WRF, including larger reductions in renal function, produced similar results (Table 2). Although not randomized interventions, interactions were not detectable between early WRF and the use of β-blockers (P = 0.92) or loop diuretics (P = 0.40) for mortality. Similarly, no significant interactions between randomization to enalapril and baseline predictors of mortality were detected (data not shown), with the exception of baseline ejection fraction (interaction P = 0.023). This interaction appeared to be predominantly driven by a greater efficacy of enalapril in patients with an ejection fraction lower than the median value of 28% (HR, 0.78; 95% CI, 0.68–0.88; P < 0.001) compared with patients with an ejection fraction higher than the median value (HR, 1.0; 95% CI, 0.88–1.2; P = 0.61).

Overall, 12.7% of the population had a reduction in dose or discontinuation of study drug within 1 month of the 14-day assessment of renal function; however, only 0.8% were coded as secondary to azotemia. Randomization to enalapril was associated with a significantly increased incidence of reduction/discontinuation of study drug for any reason (odds ratio, 1.3; P < 0.001) or azotemia (odds ratio, 2.6; P = 0.002). However, an analysis of only patients whose study drug was not dose reduced/discontinued did not change the strong

| Table 1. Baseline Patient Characteristics of the Overall Cohort and Patients With and Without WRF |
|---------------------------------------------|----------------|----------------|----------------|----------------|
| Characteristics                             | Overall Cohort | Early WRF Yes (n = 606) | Early WRF No (n = 5771) | P Value |
| Demographics                                |                | 59.3±10.2 | 59.8±10.1 | 59.3±10.2 | 0.237 |
| Age, y                                     |                | 59.8±10.1 | 59.3±10.2 | 0.237 |
| White race                                  |                | 89.1  | 88.3  | 89.2  | 0.514 |
| Male sex                                    |                | 85.7  | 82.0  | 86.1  | 0.006 |
| Medical history                             |                | 38.4  | 40.6  | 38.2  | 0.251 |
| Hypertension                                |                | 19.0  | 21.6  | 18.7  | 0.087 |
| Stroke                                      |                | 6.5   | 6.4   | 6.5   | 0.976 |
| Prior myocardial infarction                 |                | 75.2  | 73.6  | 75.4  | 0.332 |
| Physical examination findings               |                | 76.1±12.3 | 77.0±12.6 | 76.0±12.2 | 0.079 |
| Heart rate                                  |                | 119.3±16.7 | 119.1±16.5 | 119.3±16.8 | 0.685 |
| Systolic blood pressure, mm Hg              |                | 74.2±9.9  | 74.1±9.9  | 74.2±9.9  | 0.790 |
| Medications (baseline)                      |                | 32.9  | 37.1  | 32.5  | 0.020† |
| Digoxin                                     |                | 31.9  | 38.4  | 31.2  | <0.001† |
| Loop diuretic                               |                | 18.0  | 14.5  | 18.3  | 0.020† |
| β-blocker                                   |                | 6.1   | 6.8   | 6.0   | 0.439 |
| Potassium-sparing diuretic                  |                | 49.8  | 53.5  | 49.5  | 0.060 |
| Enalapril                                   |                | 139.5±3.0 | 139.4±3.0 | 139.5±3.0 | 0.447 |
| Estimated glomerular filtration rate, mL/min/1.73 m² |       | 65.6±19.1 | 79.5±28.0 | 64.1±17.3 | <0.001† |
| Proportion with estimated glomerular filtration rate <60 mL/min/1.73 m² |       | 39.8  | 22.9  | 41.6  | <0.001† |
| Blood urea nitrogen, mg/dL                  |                | 18.8±6.9 | 18.7±7.1 | 18.8±6.9 | 0.680 |
| Creatinine, mg/dL                           |                | 1.2±0.3 | 1.0±0.3 | 1.2±0.3 | <0.001† |
| Functional status/ejection fraction         |                | 27.0±6.3 | 26.4±6.4 | 27.1±6.2 | 0.011† |
| Left ventricular ejection fraction, %       |                | 1.7±0.7 | 1.8±0.7 | 1.7±0.7 | 0.001† |

*Data are given as percentage of each group unless otherwise indicated. Of the overall cohort, 9.5% had early WRF and 90.5% did not have early WRF. Early WRF was defined as a 20% reduction in GFR from baseline to 14 days after randomization.

†Significant.

*Data are given as mean±SD.
association between early WRF in the placebo group and death (adjusted HR, 1.4; 95% CI, 1.1–1.9; \( P = 0.004 \)) (goodness-of-fit test \( P = 0.26 \)) or the lack of association in the enalapril group (adjusted HR, 0.95; 95% CI, 0.7–1.3; \( P = 0.70; \ P = 0.04 \) for the interaction). The goodness-of-fit test \( P = 0.28 \) for the full interaction model. Interestingly, among patients who continued the study drug, the greatest survival advantage with randomization to enalapril vs placebo seemed to be in patients who developed early WRF (adjusted HR,

Figure 1. Kaplan-Meier curves grouped by presence or absence of early worsening renal function (WRF) and randomization to enalapril or placebo. Early WRF was defined as a 20% reduction in glomerular filtration rate from baseline to 14 days after randomization.

### Table 2. Incidence and Risk of Death Associated With Various Definitions of Early WRF in Patients Randomized to Placebo or Enalapril

<table>
<thead>
<tr>
<th>WRF Definition</th>
<th>Overall Incidence, No. (%)</th>
<th>Increase in Creatinine, Mean±SD, mg/dL</th>
<th>OR (95% CI) for WRF With Enalapril</th>
<th>Placebo Group</th>
<th>Enalapril Group</th>
<th>Adjusted Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P Value</td>
<td>P Value</td>
<td>P Value*</td>
</tr>
<tr>
<td>≥20% decrease in GFR</td>
<td>606 (9.5)</td>
<td>0.37±0.23</td>
<td>1.2 (0.99–1.4)</td>
<td>0.06</td>
<td>1.4 (1.1–1.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>≥50% decrease in GFR</td>
<td>30 (0.5)</td>
<td>0.90±0.46</td>
<td>1.5 (0.73–3.1)</td>
<td>0.26</td>
<td>2.6 (1.2–5.7)</td>
<td>0.015</td>
</tr>
<tr>
<td>≥0.3 mg/dL increase in creatinine</td>
<td>397 (6.2)</td>
<td>0.46±0.24</td>
<td>1.3 (1.1–1.6)</td>
<td>0.01</td>
<td>1.5 (1.1–1.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>≥25% increase in creatinine</td>
<td>418 (6.6)</td>
<td>0.43±0.24</td>
<td>1.1 (0.9–1.4)</td>
<td>0.28</td>
<td>1.6 (1.2–2.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Both a ≥0.3 mg/dL and a 25% increase in creatinine</td>
<td>316 (5.0)</td>
<td>0.49±0.26</td>
<td>1.2 (0.99–1.6)</td>
<td>0.06</td>
<td>1.7 (1.3–2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥0.5 mg/dL increase in creatinine</td>
<td>71 (1.1)</td>
<td>0.86±0.33</td>
<td>1.5 (0.9–2.4)</td>
<td>0.11</td>
<td>2.1 (1.3–3.6)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

All WRF definitions are calculated from change in creatinine from baseline to 14 days after randomization. Covariates were adjusted for the following: age; race; ejection fraction; heart rate; diastolic blood pressure; New York Heart Association class; serum sodium level; eGFR; history of diabetes, hypertension, stroke, or myocardial infarction; loop diuretic; potassium-sparing diuretic; digoxin; and β-blocker use. OR, odds ratio.

*Significant.
0.66; 95% CI, 0.5–0.9; P=0.018) (goodness-of-fit test
P=0.17) as opposed to the survival advantage of enalapril in
patients without early WRF (adjusted HR, 0.9; 95% CI,
0.8–1.0; P=0.10) (goodness-of-fit test P=0.46) (Figure 2).
The previously described models were adjusted for age, race,
ejection fraction, heart rate, diastolic blood pressure, New
York Heart Association class, serum sodium level, estimated GFR, history of
diabetes, hypertension, stroke, or myocardial infarction; loop diuretic; potassium-sparing diuretic; digoxin, and β-blocker use. Notably, there were no significant differences
in any baseline characteristic among patients with early WRF
assigned to enalapril vs placebo (data not shown).

**Discussion**
The primary finding of this analysis is the strong interaction
between early WRF-associated mortality and randomization
to enalapril or placebo in a large population with cardiac
dysfunction. Early WRF was associated with significantly
increased mortality in subjects randomized to placebo. How-
ever, in the group randomized to enalapril, early WRF was
free from adverse prognostic significance. Notably, the de-
development of early WRF did not appear to reduce the survival
benefit imparted by enalapril. These results provide strong
support for the concept that WRF is not a prognostically
uniform syndrome and the mechanism underlying WRF may
be critical in determining the subsequent prognosis.

The renin-angiotensin-aldosterone axis plays a critical role
in the regulation of intrarenal hemodynamics. Particularly
in the setting of heart failure, angiotensin II can have an
important role in the preservation of GFR. This results from
preferential vasoconstriction of the efferent arteriole, leading
to an increased filtration fraction and maintenance of GFR,
despite an overall decrease in renal blood flow. However,
the degree to which a compensatory increase in filtration
fraction occurs is variable; as a result, changes in GFR
secondary to ACE inhibition are highly unpredictable, with
some patients experiencing a significant reduction in GFR
and some experiencing a substantial improvement. This
interpatient variability is the result of the linear relationship
between GFR, renal plasma flow, and filtration fraction
(GFR=renal plasma flow×filtration fraction) because ACE-I
reliably causes an increase in renal plasma flow but also
causes a variable decrease in filtration fraction.

The finding of a strong differential influence of early WRF
on mortality between patients randomized to enalapril and
placebo in the setting of a small nonsignificant increase in the
incidence of early WRF can likely be explained by the previously referenced physiological principles. One possible explanation would be that initiation of enalapril did not directly cause any new cases of early WRF but somehow completely eliminated the negative prognostic effects of early WRF. This scenario seems unlikely given that ACE-I use has been prevalent in the largely contemporary populations in which WRF-associated mortality has been described. A more likely explanation is that enalapril initiation was the direct cause of some cases of early WRF, but this was offset by a lower rate of spontaneously occurring early WRF facilitated by the well-known positive effects of ACE inhibition on systemic and renal hemodynamics. As a result, despite the similar incidence of early WRF in both groups, the underlying mechanism causing early WRF may have been different, potentially explaining the differential mortality between groups.

Regardless of whether enalapril caused a shift in the underlying mechanism or mitigated the resultant mortality, the fact remains that patients randomized to enalapril did not experience increased mortality associated with early WRF, whereas those randomized to placebo had substantially worsened survival with early WRF. The exclusion of patients who had their study drug dose reduced/discontinued in proximity to the early WRF did not eliminate this finding. Furthermore, at 1 year, recovery of renal function in patients with early WRF was significant and similar between patients assigned to placebo or enalapril. Notably, the survival benefit associated with enalapril remained present in patients who developed early WRF. As a result, these data provide some reassurance that even relatively large (ie, 30%) early deteriorations in renal function after initiation of an ACE-I may not indicate an adverse clinical event or that the patient will not derive benefit from continuation of the medication. Notably, even patients with a 50% reduction in GFR (average increase in serum creatinine, 0.9 mg/dL) after enalapril initiation did not have increased mortality associated with early WRF. However, the American Heart Association scientific statement regarding ACE-I initiation in patients with heart failure recommends that an increase in serum creatinine of $\geq 0.5$ mg/dL may be an indication to discontinue ACE-I therapy.\textsuperscript{31} Although the current data indicate that further study of this phenomenon is needed, the small number of patients with large increases in creatinine in the SOLVD population limits the conclusions that can be drawn from these analyses. Thus, best clinical judgment on a case-by-case basis should be used in instances of large increases in creatinine after ACE-I initiation. Nonetheless, these data provide evidence to suggest that ACE-I therapy should not be withdrawn after an early reduction in renal function of moderate severity.

This study was a post hoc retrospective analysis; as a result, residual confounding cannot be excluded. The SOLVD trial was not designed to investigate early WRF, and, given that treating physicians were not blinded to renal data, treatment strategies were likely modified in response to these variables. It is impossible to discern what percentage of the enalapril/early WRF group had early WRF as a direct result of randomization to enalapril. Thus, there are an unknown percentage of subjects in the enalapril group who likely had spontaneous early WRF unrelated to enalapril, possibly reducing the effect size. Patients with severe renal insufficiency (creatinine level, $>2.5$ mg/dL) were excluded from SOLVD, limiting generalization to this group of patients. Although randomization to enalapril was associated with a greater survival advantage in patients who developed early WRF, this finding was the result of a postrandomization subgroup analysis and, thus, causality cannot be determined. Therefore, this result should be interpreted with caution. Although the average decrease in eGFR was not small in the early WRF group, larger potentially clinically significant deteriorations in renal function likely triggered modifications in therapy and, thus, the outcome of continuation of ACE-I in patients with large reductions in eGFR cannot be determined from this analysis. The few patients with severe heart failure also limits generalization. Although the SOLVD trials occurred before the routine use of medications, such as $\beta$-blockers and aldosterone antagonists, and replication prospectively in contemporary populations would be valuable, the lack of clinical equipoise in denying ACE-I therapy to patients with cardiac dysfunction will likely make this impossible.

**Conclusion**

In patients with left ventricular dysfunction, early WRF in the setting of ACE-I initiation is free of adverse prognostic significance, as opposed to early WRF in patients not treated with ACE-I, which is associated with significantly reduced survival. Notably, patients with early WRF in the setting of ACE-I initiation do not appear to lose the survival benefit imparted by use of the ACE-I therapy. These findings add further evidence to the notion that WRF is a heterogeneous disorder and provide reassurance that ACE-I–associated early WRF may be free of prognostic importance.

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**Disclosures**

None.

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**CLINICAL PERSPECTIVE**

Worsening renal function (WRF) has been associated with substantially worsened survival in the setting of cardiac dysfunction. However, it is unclear if this decreased survival is a direct result of the reduced glomerular filtration rate (GFR) or if WRF is simply a marker of such severe heart failure that peripheral organ dysfunction occurs. Initiation of angiotensin-converting enzyme inhibitor (ACE-I) therapy can lead to preferential vasodilatation of the efferent arteriole, with a resultant reduction in renal function. Although this physiological consequence of ACE-I initiation can produce a similar reduction in GFR as spontaneously occurring WRF, these alterations in renal hemodynamics would not be expected to directly cause adverse outcomes independent of the reduction in GFR. In this study, we investigated the relative rate of death associated with WRF in patients with left ventricular dysfunction randomized to enalapril or placebo. We found that WRF was strongly associated with death in the placebo group but had no adverse prognostic significance in patients assigned to enalapril. Notably, among patients who continued study medication despite WRF, the benefit from randomization to enalapril was particularly pronounced. Overall, these data suggest that the mechanism underlying WRF is important in determining the subsequent prognosis. Specifically, moderate reductions of GFR in the setting of ACE-I initiation appear to represent a benign event and should not necessarily trigger discontinuation of the ACE-I therapy.
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