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## Cardiorenal Interactions

### Insights From the ESCAPE Trial

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- Objectives** We examined the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) database to understand the impact and pathophysiology of renal dysfunction in patients hospitalized with advanced decompensated heart failure (HF).
- Background** Baseline renal insufficiency (RI) (estimated glomerular filtration rate [eGFR] <60 ml/min) and worsening renal function (WRF) (↑ serum creatinine [SCr] ≥0.3 mg/dl) during treatment of decompensated HF are associated with adverse outcomes.
- Methods** We used a Cox proportional hazards model to evaluate the impact of renal function on 6-month outcomes. Renal parameters were correlated with hemodynamic measurements. The impact of a strategy using pulmonary artery catheter (PAC) guidance on WRF and outcomes in patients with baseline RI was compared with treatment based on clinical assessment alone.
- Results** Baseline and discharge RI, but not WRF, were associated with an increased risk of death and death or rehospitalization. Among the hemodynamic parameters measured in patients randomized to the PAC arm (n = 194), only right atrial pressure correlated weakly with baseline SCr (r = 0.165, p = 0.03). There was no correlation between baseline hemodynamics or change in hemodynamics and WRF. A PAC-guided strategy was associated with less average increase in creatinine but did not decrease the incidence of defined WRF during hospitalization or affect renal function after discharge relative to clinical assessment alone.
- Conclusions** Among patients with advanced decompensated HF, baseline RI impacts outcomes more than WRF. Poor forward flow alone does not appear to account for the development of RI or WRF in these patients. The addition of hemodynamic monitoring to clinical assessment does not prevent WRF or improve renal function after discharge. (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization; NCT00000619). (J Am Coll Cardiol 2008;51:1268–74) © 2008 by the American College of Cardiology Foundation

There is increasing awareness of the interdependency between the heart and kidney in patients with heart failure. A number of studies have shown that abnormal renal function is associated with poor outcomes in patients with left ventricular dysfunction and heart failure (1–3). Moreover, when patients are hospitalized with heart failure exacerbation, even small changes in renal function can influence prognosis (4,5). Although the so-called “cardio-renal syn-

drome” is defined as the interaction of the heart and kidney that leads to diuretic resistance and worsening renal function, its pathophysiology is poorly understood.

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The ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial prospectively compared the strategy of pulmonary artery catheter-guided therapy (PAC) with treatment based on clinical assessment alone (CLIN) with regard to short-term and 6-month outcomes in patients hospitalized with advanced heart failure (6,7). The ESCAPE trial provides a unique opportunity to evaluate the relationship between cardiac hemodynamics and renal dysfunction in this patient population. The current study is a post-hoc examination of

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the data from the ESCAPE trial to: 1) evaluate the measure of renal function (i.e., admission creatinine/creatinine clearance [CrCl], discharge creatinine/CrCl, or worsening renal function) that has the greatest influence on outcomes in the advanced heart failure population; 2) examine the relationship between hemodynamic parameters and the above mentioned measures of renal function; and 3) assess the impact of pulmonary artery catheter-guidance on worsening renal function during heart failure hospitalization and on short- and long-term outcomes in patients with baseline renal insufficiency.

## Methods

**Study population.** The Institutional Review Boards of participating ESCAPE centers approved the study. A total of 433 patients were enrolled at 26 sites. The inclusion and exclusion criteria of patients enrolled in the ESCAPE trial have been previously described (6). For the current study, patients with a left ventricular ejection fraction  $\leq 30\%$ , recent hospitalization or escalation of out-patient diuretic therapy, and systolic blood pressure  $\leq 125$  mm Hg who were admitted to the hospital with at least 1 sign and 1 symptom of heart failure, despite adequate treatment with angiotensin-converting enzyme inhibitors and diuretics, were included. Important exclusion criteria included a creatinine  $>3.5$  mg/dl, the use of dobutamine/dopamine  $>3$   $\mu\text{g}/\text{kg}/\text{min}$  or milrinone before randomization, and requirement for early right heart catheterization.

**Study design.** Patients were randomized 1:1 to receive therapy guided by clinical assessment and the PAC or CLIN. The treatment goal in the CLIN arm was resolution of clinical signs and symptoms of congestion. The treatment goal of the PAC arm was similar with the addition of pulmonary capillary wedge pressure (PCWP)  $\leq 15$  mm Hg and right atrial pressure (RAP)  $\leq 8$  mm Hg. The protocol did not specify drug selection, but the use of inotropic agents was discouraged. Medications were titrated to avoid progressive renal dysfunction or symptomatic hypotension (7). The primary end point of the ESCAPE trial was days alive and out of the hospital for 6 months after randomization (6,7). Secondary end points relevant to the present study included 30-day mortality and length of stay (6,7). This study is a post-hoc analysis of the renal and hemodynamic data collected in the ESCAPE trial to gain further insight into cardio-renal interactions in the advanced heart failure population.

**Measures of renal function.** In the ESCAPE trial, serum creatinine (SCr) was measured at baseline, day of optimal volume status (as judged by the physician), day 7 of hospitalization, day of hospital discharge, and at 3 months and 6 months. For this study, we calculated the estimated CrCl (estimated glomerular filtration rate [eGFR]) by using the modified Modification of Diet in Renal Disease equation (8,9). Worsening renal function was defined as an increase in SCr from baseline to discharge  $\geq 0.3$  mg/dl. This

value was chosen because it has previously been demonstrated to have the maximum sensitivity and specificity for in-hospital mortality and length of stay (5).

**Statistical methods.** Values are presented as mean  $\pm$  SD. Continuous variables were compared with the Student *t* test for normally distributed and the Wilcoxon rank sum test for not normally distributed variables, respectively. Discrete variables were compared with the use of chi-square analysis. Univariate Cox proportional hazards regression analysis was used to test the

prognostic value of each renal parameter. Individuals alive and not hospitalized at 180 days were censored. The hazard ratios for SCr and eGFR were calculated for increments of 0.3 mg/dl and decrements of 10 ml/min, respectively. The hazard ratio for worsening renal function was calculated by treating it as a dichotomous variable with a positive change being an increase in SCr  $\geq 0.3$  mg/dl from baseline to discharge. To verify the prognostic value of worsening renal function, the hazard ratio for death and death or rehospitalization also was assessed for a decline in eGFR  $\geq 25\%$  from baseline to discharge. In the PAC patients, baseline hemodynamic indexes were correlated with baseline SCr, eGFR, and worsening renal function using the Pearson's correlation coefficient for normally distributed variables and Spearman's correlation coefficient for not-normally distributed data. Changes in hemodynamic indices during the hospitalization were also correlated with worsening renal function using the methods described previously. Univariate predictors of worsening renal function were evaluated by logistic regression analysis. Significant predictors were then tested in a step-wise multivariate model. A *p* value  $\leq 0.05$  was considered statistically significant.

## Results

**Baseline characteristics.** A total of 433 patients were enrolled in the ESCAPE trial. The complete baseline characteristics of the study population have been published previously (7). Baseline characteristics pertinent to this analysis are presented in Table 1. Importantly, the prevalence of hypertension and diabetes and the use of baseline medications, including dosages of loop-diuretics, did not differ between the 2 treatment groups. Baseline blood pressure and renal function also were similar between the 2 study arms.

**Measures of renal function and outcomes.** For the patients enrolled in the ESCAPE trial, the median baseline SCr was 1.50 mg/dl and the median baseline eGFR was

### Abbreviations and Acronyms

**CLIN** = clinical assessment-guided treatment strategy

**CrCl** = creatinine clearance

**eGFR** = estimated glomerular filtration rate

**PAC** = pulmonary artery catheter-guided treatment strategy

**PCWP** = pulmonary capillary wedge pressure

**RAP** = right atrial pressure

**SCr** = serum creatinine

**Table 1 Baseline Characteristics of the Study Population**

Characteristic	CLIN (n = 218)	PAC (n = 215)	p Value
Age, yrs	56 ± 14	56 ± 14	0.80
Hypertension, %	47	48	0.78
Diabetes mellitus, %	34	33	0.68
ACE-I/ARB, %	90	91	0.66
Beta-blockers, %	59	65	0.19
Aldosterone antagonist, %	44	44	0.98
Loop diuretic, mg/day	332 ± 392	306 ± 530	0.08
Weight, kg	85.6 ± 20.3	85.7 ± 21.8	0.86
Systolic BP, mm Hg	106 ± 15	106 ± 17	0.77
BUN, mg/dl	36 ± 24	34 ± 21	0.88
Serum creatinine, mg/dl	1.5 ± 0.6	1.5 ± 0.6	0.50
eGFR, ml/min	76.1 ± 40.6	72.8 ± 36.4	0.79

ACE-I/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BP = blood pressure; BUN = blood urea nitrogen; CLIN = clinical assessment-guided therapy; eGFR = estimated glomerular filtration rate; PAC = pulmonary artery catheter-guided therapy.

71.4 ml/min. The median discharge SCr and median discharge eGFR were 1.55 mg/dl and 73.9 ml/min, respectively. In the ESCAPE trial, 45% of enrolled patients had some deterioration in their renal function at the time of discharge relative to baseline with mean and median changes in SCr from baseline to discharge of 0.07 and 0.00 ml/min, respectively. A total of 110 (29.5%) patients had an increase in SCr ≥0.3 mg/dl relative to baseline.

The association between various measures of renal function and outcomes was tested. As shown in Table 2, both baseline and discharge renal function were predictive of 6-month outcomes. The risk of death and death or rehospitalization at 6 months increased with increasing SCr and decreasing eGFR. However, a change in SCr of ≥0.3 mg/dl or a decline in eGFR of ≥25% compared with baseline was not associated with an increased risk of death or death or rehospitalization at 6 months. Interestingly, baseline renal function appeared to be more predictive of long-term outcomes than worsening renal function during hospitalization.

**Hemodynamics and renal function.** In an effort to understand the relationship between cardiac and renal function in patients with advanced heart failure, we correlated baseline SCr and eGFR with baseline hemodynamic measurements in patients randomized to the PAC arm (n = 194). There

was no correlation between baseline SCr or eGFR and baseline PCWP, cardiac index, or systemic vascular resistance (data not shown). There was however, a weak, but significant, correlation between baseline SCr and RAP (r = 0.165, p = 0.03) and similarly between baseline eGFR and RAP (r = -0.195, p = 0.01).

Among the 194 patients randomized to PAC, there was no correlation between baseline hemodynamic parameters (RAP, PCWP, cardiac index, and SVR) and worsening renal function (data not shown). Similarly, there was no correlation between change in hemodynamic parameters during hospitalization and worsening renal function (data not shown).

**Effect of PAC on outcomes in patients stratified by baseline renal function.** To evaluate whether PAC improved outcomes in high-risk patients with baseline renal insufficiency, we divided the patient population into those with eGFR <60 ml/min (n = 117) and ≥60 ml/min (n = 256). The proportion of patients with eGFR <60 ml/min was similar in the 2 treatment arms (31.7% in PAC vs. 31% in CLIN). A pulmonary artery catheter-guided strategy was not associated with improved 6-month outcomes of death or death or rehospitalization in either group, relative to a strategy based on clinical examination alone (Table 3).

The impact of PAC on in-hospital mortality was not evaluated because there were only 8 in-hospital deaths in the ESCAPE trial (7). With regard to short-term outcomes, PAC did not affect 30-day mortality or length of stay in either eGFR group relative to the CLIN arm. Among patients with eGFR <60 ml/min, 3 of 59 patients died at 30 days compared with 6 of 58 in the CLIN arm (p = 0.30). Similarly, among patients with an eGFR ≥60 ml/min, there was no difference in 30 day mortality between patients randomized to the PAC (5 of 127) and CLIN (4 of 129) arms (p = 0.72). Length of stay did not differ with eGFR or treatment strategy. For patients with eGFR <60 ml/min, the median length of stay was 6 days in the CLIN arm and 7 days in the PAC arm (p = 0.88) and for those with an eGFR ≥60 ml/min, it was 6 days in both arms (p = 0.20). Thus, the addition of PAC neither shortened hospitalization nor improved outcomes in patients with baseline renal insufficiency compared to CLIN.

**Table 2 Relationship Between Renal Parameters and 6-Month Outcomes**

	Time to Death			Time to Death or Rehospitalization		
	HR*	95% CI	p Value	HR*	95% CI	p Value
Baseline SCr	1.20	1.11-1.29	<0.0001	1.14	1.08-1.21	<0.0001
Baseline eGFR	1.25	1.13-1.38	<0.0001	1.10	1.05-1.15	<0.0001
Discharge SCr	1.30	1.20-1.41	<0.0001	1.14	1.08-1.21	<0.0001
Discharge eGFR	1.28	1.14-1.43	<0.0001	1.09	1.03-1.15	0.002
≥0.3 mg/dl ↑ SCr†	1.31	0.81-2.10	0.27	1.26	0.96-1.64	0.09
≥25% ↓ eGFR‡	1.49	0.91-2.44	0.12	1.06	0.79-1.43	0.69

\*Hazard ratio (HR) calculated per 0.3-mg/dl increments in serum creatinine (SCr) and per 10-ml/min decrements in estimated glomerular filtration rate (eGFR). Worsening renal function, defined as: 1) †an increase in SCr ≥0.3 mg/dl; and 2) ‡a decrease in eGFR ≥25% from baseline to discharge, is treated as a dichotomous variable.  
 CI = confidence interval.

**Table 3** Impact of PAC on 6-Month Outcomes in Patients Stratified by Baseline Renal Function

End Point	Subgroup (eGFR, ml/min)	HR for PAC Versus CLIN	95% CI	p Value
Death	<60	1.45	0.92-2.30	0.11
	≥60	0.88	0.54-1.44	0.61
Death or rehospitalization	<60	1.17	0.90-1.52	0.23
	≥60	0.92	0.71-1.20	0.55

The p value for the interaction between eGFR and treatment was not significant for both death (p = 0.18) and death or rehospitalization (p = 0.26). Abbreviations as in Tables 1 and 2.

**Predictors of worsening renal function in the ESCAPE trial.** It has previously been suggested that an increase in creatinine during the treatment of decompensated heart failure is associated with adverse outcomes (4,5). To evaluate why patients with baseline renal insufficiency might have a worse prognosis, we evaluated the predictors of worsening parameters of renal function in the ESCAPE trial. Univariate analysis of the ESCAPE database demonstrated that baseline renal insufficiency was not predictive of the development of worsening renal function during the treatment of decompensated heart failure (p = 0.68). However, a previous history of hypertension (p = 0.0007), a previous history of diabetes mellitus (p = 0.03), and in-hospital thiazide diuretic use (p < 0.0001) were associated with an increase in SCr ≥0.3 mg/dl relative to baseline. Interestingly, neither in-hospital intravenous vasodilator use (p = 0.18) nor in-hospital loop diuretic dosage (p = 0.59) were predictive of the development of worsening renal function. Although, on average, PAC was associated with significantly less deterioration in renal function relative to the CLIN arm (p = 0.02), the proportion of patients with an increase in SCr of ≥0.3 mg/dl was similar in both the PAC and CLIN arms (26% vs. 33%, p = 0.18). Furthermore, SCr was similar in the PAC and CLIN arms at discharge (1.52 mg/dl vs. 1.58 mg/dl, p = 0.38) and 6 months' follow up (1.49 mg/dl vs. 1.59 mg/dl, p = 0.38). Only hypertension (p = 0.002) and in-hospital thiazide use (<0.0001) remained predictive of worsening renal function in the multivariable analysis.

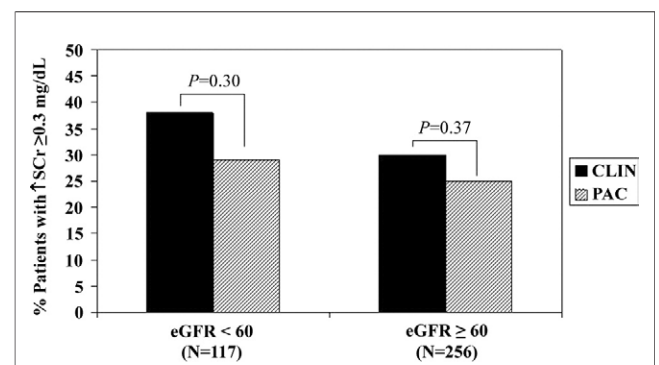
Although baseline SCr/eGFR was not a predictor of worsening renal function in this analysis, previous studies have suggested that baseline renal insufficiency is a risk factor for the development of worsening renal function during heart failure hospitalization. Therefore, we evaluated the impact of PAC on worsening renal function in patients stratified by baseline eGFR. Approximately, one-third of the patients with baseline eGFR <60 ml/min and 28% of those with baseline eGFR ≥60 ml/min developed worsening renal function (p = 0.28). The PAC did not decrease the incidence of worsening renal function in either eGFR group (Fig. 1).

**In-hospital medication use based on baseline renal function and study arm.** To see whether treatment differences might have contributed to the worse outcomes observed in patients with baseline renal insufficiency, we compared in-hospital medication use between patients with a low eGFR and those with normal renal function. Patients with

baseline renal insufficiency (eGFR <60 ml/min) were more likely to be treated with thiazide diuretics in addition to loop diuretics (39% vs. 26%, p = 0.02). Although not statistically significant, there was also a trend for higher vasodilator (35% vs. 28%) and inotrope use (51% vs. 43%) in patients with baseline renal dysfunction. Among these patients, those randomized to PAC were less likely to receive thiazides, whereas those treated according to clinical assessment alone tended to have less vasodilator and inotrope use (Table 4). These data highlight the need for additional agents to overcome diuretic resistance in patients with baseline renal insufficiency, regardless of treatment strategy.

## Discussion

This analysis from the ESCAPE trial shows that impaired baseline renal function, but not worsening renal function, is strongly associated with adverse outcomes in advanced heart failure patients admitted with acute decompensation. Despite this strong inter-relationship between cardiac and renal disease, of the hemodynamic parameters measured, only RAP had a weak correlation with baseline renal function. Attempts to optimize measured hemodynamics and end-organ perfusion using PAC did not improve renal function or outcomes



**Figure 1** Impact of PAC on Worsening Renal Function in Patients Stratified by Baseline Renal Function

Patients were stratified based on their admission estimated glomerular filtration rate (eGFR) into those with (eGFR <60 ml/min) and without (eGFR ≥60 ml/min) baseline renal insufficiency. A pulmonary artery catheter-guided treatment strategy (PAC) did not reduce the incidence of worsening renal function (defined as a ≥0.3 mg/dl increase in serum creatinine from baseline to discharge) in either eGFR group relative to a strategy based on clinical assessment alone (CLIN).

**Table 4** In-Hospital Medication Use by Baseline Renal Function and Treatment Strategy

	eGFR <60 ml/min			eGFR ≥60 ml/min		
	CLIN (n = 58)	PAC (n = 59)	p Value	CLIN (n = 129)	PAC (n = 127)	p Value
Loop diuretics, %	91	90	0.78	92	93	0.84
Thiazide diuretics, %	48	29	0.04	29	24	0.41
Intravenous vasodilators, %	28	42	0.12	16	43	<0.001
Intravenous inotropes, %	46	57	0.23	41	44	0.65
Total loop diuretic dose, mg	286.4	466.7	0.38	240.1	272.7	0.59

Abbreviations as in Table 1.

in this advanced heart failure population, relative to CLIN. These results suggest that in patients with advanced decompensated heart failure the relationship between heart failure and renal dysfunction is more complex than hemodynamics alone.

Several previous studies have evaluated the contribution of renal insufficiency to outcome in patients with left ventricular dysfunction and heart failure. In patients with asymptomatic and symptomatic left ventricular dysfunction from the SOLVD (Studies Of Left Ventricular Dysfunction) trial, Dries et al. (2) showed that moderate renal insufficiency (eGFR <60 ml/min) was associated with increased total and pump failure mortality and the combined end point of heart failure hospitalization and death. In the Digitalis Intervention Trial, which included largely New York Heart Association functional class II to III heart failure patients, Shlipak et al. (10) reported a steep increase in annual mortality when eGFR decreased to <50 ml/min/1.73 m<sup>2</sup>. McAlister et al. (11) evaluated a prospective cohort of 754 patients referred to their clinic with systolic or diastolic heart failure. Over a median follow-up period of 926 days, they found that estimated CrCl was an independent predictor of survival with a 1% increase in mortality for every 1 ml/min decrease in eGFR. Hillege et al. (12) reported similar findings from substudies of the PRIME-II (Second Prospective Randomized Study of Ibopamine on Mortality and Efficacy) (1) and CHARM (Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity) trials. The results of this analysis concur with these studies and confirm that in patients admitted with decompensated heart failure, the presence of baseline renal insufficiency portends a poor prognosis.

Worsening renal function during hospitalization also has been associated with greater in-hospital, 30-day, and 6-month mortality, longer lengths of stay, and higher hospital costs (4,13,14). Previous retrospective analyses have identified advanced age, hypertension, diabetes, pre-existing renal insufficiency, and higher doses of loop diuretics as potential risk factors contributing to the development of worsening renal function (4,14,15). To our knowledge, this is the first analysis to prospectively evaluate the incidence of worsening renal function and its impact on mortality and rehospitalization in the advanced heart failure population. As in previous studies, the incidence of worsening renal function (defined as an increase in SCr ≥0.3 mg/dl) was

approximately 30% (4,14). Similarly, hypertension, diabetes, and the use of thiazide diuretics were associated with the development of worsening renal function. However, in this analysis worsening renal function did not predict an inferior prognosis in this patient population. This may have important clinical implications, because the current trend in in-hospital management is to curtail diuresis and withdraw important life-prolonging medications, such as angiotensin-converting enzyme inhibitors, in the face of worsening renal function during hospitalization. Perhaps this outcome is inevitable in patients with risk factors such as hypertension and diabetes and should be viewed as a marker of intrinsic renal disease rather than a signal to limit adequate diuresis and symptom resolution. Further prospective studies are needed to clarify the prognostic significance of worsening renal function relative to baseline renal insufficiency in the advanced heart failure population.

Renal dysfunction, in the absence of heart failure, carries a poor prognosis (16). It is not surprising, therefore, that the concomitant presence of 2 diseases with poor outcomes compounds the mortality of either alone. However, it is interesting to examine the potential reasons why patients with advanced heart failure have an increased incidence of concomitant renal dysfunction (17). The ESCAPE trial provides a unique opportunity to better understand the relationship between cardiac and renal dysfunction at a hemodynamic level. The lack of correlation between baseline renal function and cardiac index in this study suggests that renal insufficiency that frequently accompanies heart failure is not merely a consequence of poor forward flow. In the ESCAPE trial, PAC improved cardiac index significantly from 1.9 ± 0.6 l/min/m<sup>2</sup> to 2.4 ± 0.7 l/min/m<sup>2</sup> (p < 0.01) (7). Yet, hemodynamic optimization with PAC did not improve renal function or long-term outcomes in this patient population. Similarly, it has been proposed that excessive vasodilation with afterload reducing agents contributes to renal dysfunction in this advanced heart failure population. Once again, the lack of correlation between SVR and baseline renal function suggests that this is probably not always the case. The weak positive correlation with RAP observed in this study does, however, suggest that biventricular failure rather than isolated left ventricular failure may be a marker of more advanced cardiac disease and thus may contribute to the development of renal insufficiency in these patients. Similarly, baseline hemody-

namics or change in hemodynamics with treatment did not correlate with the development of worsening renal function during hospitalization. This again suggests that a “pre-renal” etiology, either on the basis of low forward flow, overdiuresis, or excessive vasodilation is unlikely to be the primary determinant of worsening renal function.

Other possible explanations for the increased incidence of renal insufficiency in patients with advanced heart failure include the observation that patients with renal dysfunction tend to be older and have a higher prevalence of comorbidities such as hypertension and diabetes that cause both intrinsic renal disease and heart failure (17). Second, the presence of these diseases, especially hypertension, disrupts renal blood flow autoregulation, making the kidney more susceptible to developing worsening renal function during the treatment of heart failure. In patients with a history of hypertension, the renal autoregulatory curve shifts to the right such that decreases in mean arterial pressure as a consequence of decreased forward flow, vasodilator medications, or diuretics result in decreased intraglomerular pressure and GFR at blood pressures that would not affect renal function in normal subjects (18,19). This is corroborated by our observation that hypertension and thiazide diuretics in addition to loop diuretics are associated with worsening renal function. Unfortunately, the number of subjects with hypertension and diabetes in ESCAPE was too small to evaluate whether PAC improves renal function and outcomes in this subset of patients. We attempted to overcome this limitation by assessing the impact of PAC in patients with baseline renal insufficiency compared to those with normal renal function. Our results demonstrate that PAC does not reduce the incidence of worsening renal function or improve renal function and outcomes in patients with baseline renal insufficiency. Coupled with the hemodynamic analysis, these results suggest that risk factors for intrinsic renal disease probably make the kidney more susceptible to cardiac compromise and thus have a greater influence on cardiorenal interactions than low output alone. Third, baroreceptor dysfunction and neurohormonal activation, such as that seen with advanced heart failure, results in inappropriate vasoconstriction of the pre-glomerular afferent arterioles, thus decreasing renal blood flow and GFR (19). Improving hemodynamics, without necessarily altering the neurohormonal milieu, probably does not affect renal function or long-term outcomes in this patient population. In the ESCAPE trial, a similar proportion of patients in the PAC arm were on neurohormonal modifiers such as angiotensin-converting enzyme inhibitors and beta-blockers at the time of hospital discharge as in the CLIN arm (7). This may explain why PAC had no impact on long-term renal function or prognosis relative to CLIN.

**Study limitations.** There are several limitations to this study. First, the ESCAPE trial was not designed to study patients with end stage or advanced renal insufficiency and the entry criteria excluded patients with creatinine >3.5 mg/dl. Second, there were insufficient patients with comor-

bidities that contribute to intrinsic renal disease, and thus it was not possible to assess whether a specific treatment strategy would be beneficial in this high-risk population. It is possible that the impact of PAC may have been more apparent in a population selected for intrinsic renal disease. Third, changes in renal function were not pre-specified end points of the ESCAPE trial and how the clinicians chose to modify therapy might have been different among investigator sites. For example, some investigators may have chosen to modify a clinical or hemodynamic parameter at the expense of worsening renal function. The opposite may have also been true. However, the data collection was not designed to determine how renal function was used to guide therapy. Unfortunately, this is true of all studies that have evaluated renal function during heart failure treatment and prospective studies in this area are needed to evaluate whether worsening renal function per se impacts outcomes. Fourth, SCr and eGFR may not be the most accurate markers for acute changes in renal function. Other markers such as cystatin-C (20) were not measured in the ESCAPE trial. Finally, a strategy that adjusts treatment based on a very limited monitoring period in hospital may not be sufficient to affect renal function or outcomes in the months after discharge, when changes in diuretic doses are frequent and are made in response to clinical assessment alone (21).

## Conclusions

This analysis of the ESCAPE trial suggests that in patients hospitalized with advanced decompensated heart failure, baseline renal insufficiency impacts prognosis more than worsening renal function during hospitalization. The lack of correlation between measured hemodynamic parameters and renal function suggests that poor forward flow may contribute to but is not the primary cause of renal dysfunction in patients with advanced heart failure. Accordingly, hemodynamic optimization with PAC did not reduce the incidence of worsening renal function or improve renal function or outcomes, even among patients with baseline renal insufficiency, in this study. Advanced heart failure patients with conditions such as hypertension and diabetes that contribute to the development of intrinsic renal disease and disrupt renal autoregulation may be at increased risk for adverse outcomes. Efforts to reverse or improve renal impairment in high-risk populations during the management of decompensated heart failure warrant further study.

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