Prevalence and Prognostic Value of Elevated Urinary Albumin Excretion in Patients With Chronic Heart Failure

Data From the GISSI-Heart Failure Trial

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**Background**—Increased urinary excretion of albumin is an early sign of kidney damage and a risk factor for progressive cardiovascular and renal diseases and heart failure. There is, however, only limited information on the prevalence and prognostic role of urinary albumin excretion in patients with established chronic heart failure.

**Methods and Results**—A total of 2131 patients enrolled in 76 sites participating in the GISSI-Heart Failure trial provided a first morning spot sample of urine at any of the clinical visits scheduled in the trial to calculate the urinary albumin-to-creatinine ratio. The relation between log-transformed urinary albumin-to-creatinine ratio and all-cause mortality (428 deaths, time from urine collection to event or censoring) was evaluated with Cox multivariable models adjusted for all significant risk factors at the time of urine collection, in the study population, and in patients without diabetes or hypertension. Almost 75% of the patients had normal urinary albumin excretion, but 19.9% had microalbuminuria (30 to 299 mg/g creatinine) and 5.4% had overt albuminuria (>300 mg/g). There was a progressive, significant increase in the adjusted rate of mortality in the study population (hazard ratio, 1.12; 95% CI, 1.05 to 1.18 per 1-U increase of log(urinary albumin-to-creatinine ratio), \( P=0.0002 \)) and in the subgroup of patients without diabetes or hypertension. Randomized treatments (n-3 polyunsaturated fatty acids or rosuvastatin) had no major impact on albumin excretion.

**Conclusions**—Independently of diabetes, hypertension, or renal function, elevated albumin excretion is a powerful prognostic marker in patients with chronic heart failure. (Circ Heart Fail. 2010;3:65-72.)

**Key Words:** heart failure ■ kidney ■ prognosis ■ microalbuminuria

Increased urinary excretion of albumin is an early sign of kidney damage and is a recognized risk factor for progressive cardiovascular and renal disease. The marker is widely used to detect individuals with undiagnosed chronic kidney disease who are at risk for cardiovascular disease. Abnormal urinary excretion may be a marker of risk even in apparently healthy people because it reflects vascular damage in the kidneys and systemic endothelial dysfunction. Microalbuminuria has been associated with an increased incidence of adverse cardiovascular outcomes in the community and after exclusion of individuals with prevalent hypertension or diabetes. Abnormal urinary excretion of albumin clusters with established risk factors for heart failure (HF), predicting HF hospitalization in patients with type 2 diabetes, is an independent predictor of incident chronic HF in the community or in patients with diabetes. When the present prospective study was planned, there was limited information on the prevalence and prognostic role of urinary albumin excretion in patients with established chronic HF. An early report showed that urinary albumin excretion was higher in 13 patients with chronic HF than in healthy control subjects. Another study found microalbuminuria in 32% of 91 patients with stable chronic HF, but it was not associated with renal function or neurohormonal activation and could not be related to outcome.

**Clinical Perspective on p 72**

albumin excretion was higher in 13 patients with chronic HF than in healthy control subjects. Another study found microalbuminuria in 32% of 91 patients with stable chronic HF, but it was not associated with renal function or neurohormonal activation and could not be related to outcome.
Unadjusted hazard ratios (HRs) using log-transformed UACR were calculated with univariate Cox proportional hazards models. An increase in the relationship between UACR and outcome was assessed by plotting the HR for mortality for each decile of UACR, using patients with UACR below 1.5 mg/g as the reference category. Cumulative survival estimates were presented as Kaplan–Meier curves for the 3 categories of albumin excretion and compared using the log-rank test. Adjusted estimates of the association between increasing albumin excretion and outcome were then obtained with Cox multivariable regression models, adjusting for any demographic and clinical variables at the time of urine collection that had a univariate relationship with outcome with \( P < 0.05 \) (age, sex, NYHA class, left ventricular ejection fraction, etiology of HF, systolic and diastolic blood pressures, heart rate, prescription of angiotensin-converting enzyme inhibitors, \( \beta \)-blockers or diuretics, atrial fibrillation, chronic obstructive pulmonary disease or diabetes, serum concentrations of potassium, creatinine, and triglycerides). The same statistical models were fitted in patients without diabetes or hypertension. The proportionality and linearity of hazards was checked by inspection of the graphs and by a time-dependent covariate test. The Martingale residuals plot was used to decide whether an independent continuous covariate could be entered directly into the model or if it had to be transformed.

The impact of the 2 randomized treatments (n-3 PUFA versus placebo and rosuvastatin versus placebo) on urinary albumin excretion was evaluated in 2 ways. First, between-treatments differences in median UACR were compared with Wilcoxon rank sum test for the 2131 patients who gave a single urine sample during the study. Second, within-patient differences of absolute changes in UACR were compared separately for the 2 experimental arms in the 215 patients randomized to n-3 PUFA versus placebo and in the 143 randomized to rosuvastatin versus placebo, whose urine samples were collected at randomization and after 3 months of follow-up, using rank ANCOVA (nonparametric analysis of covariance), controlling for the baseline value.

Statistical analysis was done using SAS version 9.1 (SAS Institute, Cary, NC). A two-sided \( P \) value of <0.05 was deemed to be statistically significant.

Results

Baseline Characteristics of the Patients

Baseline characteristics of the patients are presented in Table 1 and are similar to those of patients enrolled in the GISSI-HF trial (data not shown). Median UACR was 8.7 mg/g creatinine (1.5 to 30.9 mg/g creatinine) (minimum, 1.5 mg/g; maximum, 7867 mg/g; Table 1), and distribution was positively skewed. Almost 75% of the patients had a normal level of urinary albumin excretion but 19.9% had microalbuminuria and 5.4% overt albuminuria (\( \geq 300 \) mg/g). Patients with high albumin excretion were older, more frequently with a severe NYHA class, hypertension, diabetes, or chronic obstructive pulmonary disease (Table 1). They had higher heart rate and systolic blood pressure and were prescribed \( \beta \)-blockers less frequently and calcium antagonists more frequently. They had higher serum concentrations of creatinine and fibrinogen.
The Prognostic Value of Urinary Albumin Excretion

In all, 428 patients died during the follow-up. Compared with survivors (n=1703), patients who died were older, leaner, more frequently males, with HF of ischemic etiology, and in a more severe NYHA class. A history of diabetes, atrial fibrillation, or chronic obstructive pulmonary disease was significantly more frequent among the patients who died. β-Blockers were prescribed more to the survivors; the opposite was true for diuretics. Serum concentrations of creatinine, bilirubin, and fibrinogen were higher in nonsurvivors. Median albumin excretion was significantly lower in survivors (7.6 [1.5 to 25.0] mg/g) than in those who died (15.8 [4.8 to 74.1] mg/g, P<0.0001). Similarly, albumin excretion was normal in more survivors (77.8% versus 62.4%), whereas more of the patients with microalbuminuria (27.6% versus 17.9%) or albuminuria (10.1% versus 4.3%) died (P<0.0001).

The rate of mortality rose significantly across deciles of albumin excretion (from 12.6% in the first to 33.8% in the last decile, χ²=61, P<0.0001, Figure 2). Interestingly, the risk also increased within the “normal” albumin excretion ratio (0 to 30 mg/g): the unadjusted HR for mortality was significantly different from unity, starting from the sixth decile (UACR, 15.3 to 23.1 mg/g) compared with the reference category (Figure 2).

Kaplan–Meier curves showed increasing mortality across the 3 categories of albumin excretion (log-rank test P<0.0001,
The relation between albumin excretion and mortality was tested by Cox proportional hazard models, entering UACR as either a continuous (log(UACR)) or a categorical variable (normal, microalbuminuria, and albuminuria). Univariate analysis indicated an increased risk of 1.21 (1.15 to 1.27) per 1-U increase of log(UACR) ([HR] [95% CI] for log(UACR)) is shown for the 561 patients with UACR below the detection limit (<1.5 mg/g creatinine), set as the reference category. The UACR range for each decile is reported below the graph (152 to 160 patients per decile). Bars indicate the range of normal albumin excretion, microalbuminuria (MA), and albuminuria (A). $\chi^2=61$, $P<0.0001$.

Figure 3. The unadjusted mortality rates were 16.8% (267 deaths of 1592 patients at risk), 27.9% (118 of 423), and 37.1% (61, 116, 423) or albuminuria (n = 423) or albuminuria (n = 116) is shown. Log-rank test, $P<0.0001$.

The relation between albumin excretion and mortality was assessed separately in the subgroup of 772 patients without diabetes or hypertension at study entry. Compared with the study population, these patients were slightly younger (65±11 years versus 67±11 years), were less frequently female (14.8% versus 21.1%), or in NYHA classes III to IV (24.5% versus 30.1%). The proportion of HF of ischemic etioloogy was lower (48.6% versus 50.8%), and the mean left ventricular ejection fraction was slightly lower (32±8% versus 33±9%, 93.7% of patients with left ventricular ejection fraction ≤0.40). Serum creatinine (1.10±0.40 mg/dL versus 1.18±0.40 mg/dL) and the proportion of patients with a low eGFR (<60 mL/min/1.73 m$^2$=25.9% versus 35.7%) were lower than in the study population.

The median UACR was significantly higher in the 556 patients (26%) with a history of diabetes (18.7 mg/g [5.4 to 98.0 mg/g], 29% with microalbuminuria, 12% with albuminuria) than in those without diabetes at enrolment (7.1 mg/g [1.4 to 21.4 mg/g], $P<0.0001$; 17% with microalbuminuria, 3% with albuminuria). Similarly, the median UACR was significantly higher in the 1183 patients (56%) with a history of hypertension (9.9 mg/g [1.5 to 38.4 mg/g], 22% with microalbuminuria, 6% with albuminuria) than in those without hypertension at enrolment.

**Sex-Specific Cutoff Values for Albumin Excretion**

The prognostic value of elevated albumin excretion was evaluated using sex-specific cutoff values. In men, albumin excretion was considered normal if UACR was <17 mg/g, microalbuminuria for UACR was 17 to 249 mg/g, and albuminuria for UACR was ≥250 mg/g. Corresponding values were 25 and 355 mg/g in women. With these cutoff values, the prevalence of normal albumin excretion, microalbuminuria, and albuminuria was 65.8%, 28.4%, and 5.8%, respectively. Kaplan–Meier curves showed increasing mortality across the 3 categories of albumin excretion (log-rank test $P<0.0001$) and unadjusted mortality rates were 16.0% (224 deaths of 1401 patients at risk), 26.7% (162 of 606), and 33.9% (42 of 124) in patients with normal albumin excretion, microalbuminuria, and albuminuria, respectively (Cochran-Armitage trend test, $P<0.0001$).

The prognostic role of urinary albumin excretion in patients without diabetes or hypertension was assessed at the time of urine collection, UACR remained independently associated with mortality (HR, 1.12 [1.05 to 1.18] per 1-U increase of log(UACR) (P=0.0002). This model included variables associated with diabetes (history of diabetes), hypertension (systolic and diastolic blood pressures), and renal function (serum creatinine concentration). Patients with microalbuminuria (HR, 1.42 [1.11 to 1.81]) and albuminuria (HR, 1.70 [1.16 to 2.50]) had a significantly higher risk of mortality than those with normal albumin excretion, taken as the reference group ($P=0.04$ and 0.006).

Figure 2. All-cause mortality and 95% CIs for mortality by deciles of UACR. Unadjusted rate of mortality (HR [95% CI] for log(UACR)) is shown for the 561 patients with UACR below the detection limit (<1.5 mg/g creatinine), set as the reference category. The UACR range for each decile is reported below the graph (152 to 160 patients per decile). Bars indicate the range of normal albumin excretion, microalbuminuria (MA), and albuminuria (A). $\chi^2=61$, $P<0.0001$. 

Figure 3. Cumulative Kaplan–Meier curves for mortality. Cumulative mortality in patients with normal albumin excretion (UACR <30 mg/g, n = 1592), microalbuminuria (UACR, 30 to 299 mg/g, n = 423) or albuminuria (UACR ≥300 mg/g, n = 116) is shown. Log-rank test, $P<0.0001$. 

The relation between albumin excretion and mortality was assessed separately in the subgroup of 772 patients without diabetes or hypertension at study entry. Compared with the study population, these patients were slightly younger (65±11 years versus 67±11 years), were less frequently female (14.8% versus 21.1%), or in NYHA classes III to IV (24.5% versus 30.1%). The proportion of HF of ischemic etioloogy was lower (48.6% versus 50.8%), and the mean left ventricular ejection fraction was slightly lower (32±8% versus 33±9%, 93.7% of patients with left ventricular ejection fraction ≤0.40). Serum creatinine (1.10±0.40 mg/dL versus 1.18±0.40 mg/dL) and the proportion of patients with a low eGFR (<60 mL/min/1.73 m$^2$=25.9% versus 35.7%) were lower than in the study population.

The median UACR was significantly higher in the 556 patients (26%) with a history of diabetes (18.7 mg/g [5.4 to 98.0 mg/g], 29% with microalbuminuria, 12% with albuminuria) than in those without diabetes at enrolment (7.1 mg/g [1.4 to 21.4 mg/g], $P<0.0001$; 17% with microalbuminuria, 3% with albuminuria). Similarly, the median UACR was significantly higher in the 1183 patients (56%) with a history of hypertension (9.9 mg/g [1.5 to 38.4 mg/g], 22% with microalbuminuria, 6% with albuminuria) than in those without hypertension at enrolment.
Table 2. Multivariable Cox Models for Mortality in the Study Population and in the Subgroup of Patients Without Diabetes or Hypertension at Study Entry

<table>
<thead>
<tr>
<th>Variable (Category or Increment)</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log (UACR) (1 unit)</td>
<td>1.21 (1.15 to 1.27)</td>
<td>&lt;0.0001</td>
<td>1.21 (1.10 to 1.32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Multivariable model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log (UACR) (1 unit)</td>
<td>1.12 (1.05 to 1.18)</td>
<td>0.0002</td>
<td>1.10 (0.99 to 1.22)</td>
<td>0.08</td>
</tr>
<tr>
<td>Age (1 y)</td>
<td>1.04 (1.03 to 1.06)</td>
<td>&lt;0.0001</td>
<td>1.03 (1.01 to 1.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>β-blockers (yes)</td>
<td>0.67 (0.53 to 0.83)</td>
<td>0.0003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log (serum creatinine) (1 unit)</td>
<td>2.16 (1.57 to 2.97)</td>
<td>&lt;0.0001</td>
<td>2.67 (1.38 to 5.15)</td>
<td>0.004</td>
</tr>
<tr>
<td>NYHA class (III to IV vs II)</td>
<td>1.38 (1.10 to 1.74)</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (females)</td>
<td>0.72 (0.54 to 0.96)</td>
<td>0.03</td>
<td>0.47 (0.25 to 0.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diuretics (yes)</td>
<td>1.80 (1.08 to 3.00)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (1 bpm)</td>
<td>1.01 (1.00 to 1.02)</td>
<td>0.01</td>
<td>1.02 (1.00 to 1.03)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Discussion

In this study, albumin excretion was measured in a large and contemporary population of patients with chronic HF (>2000 individuals). The novel findings can be summarized as follows: the prevalence of abnormal albumin excretion was 25%, very similar to that of the patients with diabetes in this population. Mortality increased proportionally with the excretion of albumin and started to be significantly elevated from UACR that are considered within the normal range. Elevated albumin excretion was a powerful prognostic marker, independent of diabetes, hypertension, or serum creatinine. The two randomized experimental treatments, rosuvastatin and n-3 polyunsaturated fatty acids did not seem to profoundly change albumin excretion rate in the limited number of patients with repeated sampling of urine.

Individuals with chronic HF in the community are most likely to be old and have concomitant comorbidities that both contribute to the cause of the disease and have an important role in its progression and response to therapy. Two frequent comorbidities, hypertension and diabetes, are associated with renal dysfunction and generalized endothelial dysfunction that may contribute to abnormalities in blood protein filtration. It is, therefore, not unexpected to see that in our population of patients with chronic HF, the prevalence of elevated urinary excretion of albumin (corresponding to the clinical categories of microalbuminuria and albuminuria) was 25%, which clusters mainly in patients with a history of diabetes and/or hypertension. It was less obvious that abnormal urinary albumin excretion could also be an independent marker of mortality in these patients.

We show here that a simple measurement of urine albumin provides strong prognostic information, independent of comorbidities that directly affect renal filtration. Indeed, the pathophysiological factors that can lead to reduced eGFR or albuminuria in HF are in part common but may also be specific. Interestingly, the risk of death rose steadily with albumin excretion and was already significantly elevated in a range of UACR considered to be within normal limits (15 to 30 mg/g), as recently found. Community-based studies have suggested a linear relationship between urinary albumin excretion and the risk of cardiovascular events or HF, even at very low levels, well below the conventional threshold for microalbuminuria.
croalbuminuria and the incidence of venous thromboembolism has been found, even in the normal range of urinary albumin excretion. The relationship between albumin excretion and mortality in our study held after multiple adjustments and in a subgroup of patients without a history of hypertension and/or diabetes. The mechanisms linking elevated albumin excretion and HF are not completely understood (and may be different from those involved in patients with diabetes) but probably encompass interplay with renal function (abnormalities of glomerular endothelial function) and more generalized endothelial dysfunction, a known risk factor for HF. The prevalence and prognostic value of albuminuria have also been investigated in patients with HF from the Candesartan in Heart Failure: Assessment of Reduction in Mortality Program. Although there are some differences in the demographic and clinical characteristics of the 2 populations (North American patients for Candesartan in Heart Failure: Assessment of Reduction in Mortality, Italian patients for GISSI-HF) or in the definition of microalbuminuria and albuminuria, both studies have enrolled a comparable number of patients and reached remarkably concordant conclusions regarding the high prevalence and negative prognostic value of elevated albumin in chronic HF.

The impact of the 2 experimental treatments (n-3 PUFA and rosuvastatin) on albumin excretion is also not yet clearly understood and, to the best of our knowledge, has not been thoroughly investigated in patients with chronic HF. A recent meta-analysis on the effects of statins on albumin excretion in patients with diabetes or kidney diseases found strong heterogeneity among the 15 studies considered (1384 patients overall), with statins achieving greater reductions in patients with higher baseline levels. However, in the largest study (864 individuals from a general population in the city of Groningen, the Netherlands; median albuminuria, 22 to 24 mg/24 h), pravastatin did not reduce albumin excretion. Some concerns are now being expressed about the effects of statins on renal handling of proteins. A transient dipstick-positive proteinuria was reported after relatively high doses, but it did not worsen renal function. Urinary excretion of α1 microglobulin, but not albumin, also rises in a dose-dependent manner in hyperlipidemic patients treated with a statin. This indicated a reduction of protein reabsorption by the proximal tubular cells, as observed in isolated kidney cells.

In the present study, using daily dose of 10 mg of rosuvastatin, we saw no real differences in albumin excretion compared with placebo. In a recent trial, rosuvastatin did not improve outcome or renal function in patients undergoing maintenance hemodialysis. Similarly, treatment with n-3 PUFA did not affect albumin excretion. Again, there are only few reports on the effect of n-3 PUFA on microalbuminuria. Supplementation with eicosapentaenoic acid (one of the n-3 PUFA extracted from fish oil) for 48 weeks at the dose of 1.8 g daily significantly reduced albumin excretion in 21 patients with diabetic peripheral neuropathy. Three months of supplementation with n-3 PUFA (3.6 g daily, 57.4% eicosapentaenoic acid and 28.7% docosahexaenoic acid) marginally reduced absolute albumin excretion but not UACR in 24 patients with type 2 diabetes mellitus. Our study suggests that, at the dosage used and for the observation time considered, the two treatments had no obvious harmful or beneficial effects on albumin excretion. This is in line with their good safety profile on renal function in the GISSI-HF trial or in clinical practice. This observation is, however, weakened by the limited number of participants with repeated determination of albumin excretion and needs to be confirmed in studies formally evaluating the effects of pharmacological therapies on albumin excretion in patients with chronic HF. Candesartan, an ARB, had no effect on albuminuria in the subset of patients with serial measurements in the Candesartan in Heart Failure: Assessment of Reduction in Mortality Program.

Study Limitations
There are some limitations to this study. First, urine was collected at variable intervals after enrollment. However, the timing of exposure was defined as the interval of time from urine collection to event or censoring, and the covariates used in the statistical models were those reported at the time of albumin measurement. We also verified that the time elapsed between randomization and urine collection was similar for patients who died and those who survived and that collection time was not a confounder in the relationship between albumin excretion and outcome. Second, since timed urine collection is cumbersome in a multicenter setting, first morning spot collection was preferred for ease of implementation, better compliance, and to minimize the influence of circadian rhythm. Third, prolonged frozen storage of urine samples may lead to various changes in albumin, underestimate the number of patients with abnormal excretion of albumin and affect its prediction of outcome. However, frozen urine samples are often used in large multicenter studies where albuminuria is determined by a central laboratory and our samples were kept at −70°C. Fourth, albumin excretion was indexed to creatinine to calculate the UACR. Recent findings have in fact shown that measuring UACR in a first morning urine sample is a good alternative to 24-hour albumin excretion for predicting cardiovascular mortality and morbidity. Fifth, virtually all study participants were whites, and the results obtained here have to be confirmed in patients of different ethnicities.

Conclusion
Urinary albumin excretion emerges here as a strong independent predictor of mortality. Recently, the ONTARGET (Renal Outcomes With Telmisartan, Ramipril, or Both, In People at High Vascular Risk) study showed that albuminuria was lowered in people at high vascular risk more by a combination of an ARB and an angiotensin-converting enzyme inhibitors than with either monotherapy, despite more frequent elevation of serum creatinine or dialysis, casting some doubts on the validity of albumin excretion as a surrogate end point for renoprotection. The patients enrolled in the GISSI-HF trial were intensively treated with drugs that should reduce urinary albumin excretion (93% were given an angiotensin-converting enzyme inhibitors or an ARB). In a scenario where n-3 PUFA and rosuvastatin do not seem to have profound effects, it is not known whether additional pharmacological interventions can further reduce albumin
excretion and if this marker can still be used as a target for guiding therapy in chronic HF. In other words, the robust findings on the prognostic value of urinary albumin excretion obtained in a population maximally treated do not provide a clue on the practical use of this marker for the management of patients with chronic HF.

Appendix

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Abnormal urinary excretion of albumin is an early sign of kidney damage stemming from vascular injury, systemic and glomerular hypertension, and inflammatory processes. It also is a recognized risk factor for the progression of cardiovascular and renal diseases. We prospectively evaluated the prognostic role of elevated urinary excretion of albumin (as a continuous or categorical variable) in >2000 patients with chronic heart failure enrolled in the GISSI-Heart Failure trial. Almost 20% had microalbuminuria, whereas 5% had overt albuminuria. There was a continuous increase in the risk of mortality in the study population (adjusted hazard ratio, 1.12 [95% CI, 1.05 to 1.18]) per 1-U increase of the log of the ratio between urine albumin and creatinine), after adjusting for demographic and clinical variables, including the presence of diabetes or hypertension. The risk was increased in a range of albumin excretion considered normal (UACR 30 mg/g).

Three-month therapy with the experimental treatments tested in the GISSI-Heart Failure trial (n-3 PUFA, 1 g/d and rosuvastatin, 10 mg/d) had no major impact on albumin excretion. Therefore, urinary albumin excretion emerges as a strong, independent predictor of mortality, as recently reported by the CHARM Programme. The patients enrolled in the GISSI-Heart Failure trial were intensively treated with drugs that should reduce urinary albumin excretion. The robust findings on the prognostic value of urinary albumin excretion obtained in a population maximally treated do not provide a clue on the practical use of this marker for the management of patients with chronic heart failure, an issue that deserves further attention.
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_Circ Heart Fail._ 2010;3:65-72; originally published online October 22, 2009;
doi: 10.1161/CIRCHEARTFAILURE.109.881805

_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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