Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure. Data from the GISSI-Heart Failure (GISSI-HF) trial

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*A complete list of the investigators who participated in the study is presented in the appendix.

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Abstract

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 (HF). There is however, only limited information on the prevalence and prognostic role of urinary albumin excretion in patients with established chronic HF.

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 (UACR). The relation between log-transformed UACR 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 [30-299 mg/g creatinine] and 5.4% overt albuminuria [≥300 mg/g]. There was a progressive, significant increase in the adjusted rate of mortality in the study population (HR [95%CI] = 1.12 [1.05-1.18] per 1 unit increase of log(UACR), 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 HF.

Key words: heart failure, albumin, urine, prognosis, microalbuminuria
Abbreviations

ACEi, angiotensin-converting enzyme inhibitors
ARB, angiotensin II type 1 receptor antagonists
COPD, chronic obstructive pulmonary disease
GISSI-HF, GISSI-Heart Failure
HF, heart failure
LVEF, left ventricular ejection fraction
n-3 PUFA, n-3 polyunsaturated fatty acids
NYHA, New York Heart Association
UACR, urinary albumin-to-creatinine ratio
Statins, HMG-CoA reductase inhibitors
Introduction

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 (1). 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 (2). Microalbuminuria has been associated with an increased incidence of adverse cardiovascular outcomes in the community (3-6), and after exclusion of individuals with prevalent hypertension or diabetes (7). Abnormal urinary excretion of albumin clusters with established risk factors for heart failure (HF), predicting HF hospitalization in type 2 diabetics (8), and is an independent predictor of incident chronic HF in the community (9,10) or in diabetics (11). 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 (12). Another study (13) 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 because of the limited sample size. Very recently, a report from the Candesartan in Heart Failure: Assessment of Reduction in Mortality (CHARM) Programme showed that elevated albumin excretion is a powerful and independent predictor of poor prognosis in 2310 patients with HF from North America (14).

A number of randomized controlled trials have shown that reducing urinary albumin excretion pharmacologically may be efficient for renal and cardiovascular protection. Reduction of urinary albumin excretion with ACE inhibitors (ACEi), angiotensin II type 1 receptor antagonists (ARB) or HMG-CoA reductase inhibitors (statins) does indeed improve the prognosis in patients
with hypertension (15) or diabetes (16). However, the impact on albumin excretion of pharmacological therapies used in chronic HF is not clear. Therefore, the main objectives of the present study were to measure the prevalence of abnormal urine excretion of albumin and to assess its prognostic role in a large, contemporary population of patients with chronic HF enrolled in a randomized multicenter clinical trial. As a secondary objective, the effects of randomized treatments (n-3 PUFA and rosuvastatin) on albumin excretion were evaluated in a subgroup of participants.
Patients and methods

The design and main results of the GISSI-HF trial have been described in detail elsewhere (17-19). Briefly, it was a randomized, double-blind, placebo controlled, multicenter study that enrolled 6975 patients with clinical evidence of chronic, stable HF (NYHA II-IV), irrespective of the cause, of the level of left ventricular ejection fraction (LVEF), and age. Patients were randomly assigned in a nested design to n-3 PUFA 1 g daily or placebo, and for those eligible, to rosuvastatin 10 mg daily or placebo. The institutional review committee at each participating center approved the study, and all patients gave informed consent.

A total of 2131 patients from 76 sites provided a first morning spot sample of urine at any of the clinical visits scheduled in the trial. In a subset of 214 patients, morning urine samples were collected at randomization and again after three months. Urine samples were transported on dry ice to the central laboratory, where they were stored at -70°C until analysis. The samples were gently thawed, centrifuged and assayed for albumin with a nephelometric method (Beckman Coulter - Immage) and creatinine with the Jaffé method (Instrumentation Laboratory - ILab Chemistry Systems). Total coefficients of variation for albumin assay were 9.8% (mean concentration of 5.60 mg/L), 5.4% (22.50 mg/L) and 2.3% (31.90 mg/L). Total coefficients of variation for creatinine assay were 5.4% (0.90 g/L) and 1.1% (4.00 g/L). The detection limits were 2.5 mg/L and 0.01 g/L for albumin and creatinine, respectively. All the assays were done in a single batch, blind.
Statistical methods

Albumin excretion was indexed to creatinine and expressed as the urinary albumin-to-creatinine ratio (UACR, mg/g creatinine), with a limit of detection of 1.5 mg/g. UACR was either considered as a continuous or a categorical variable, in three classes: normal (UACR < 30 mg/g), microalbuminuria (UACR 30-299 mg/g) and albuminuria (UACR ≥ 300 mg/g). The differences in baseline demographic and clinical characteristics between patients who experienced the primary outcome of all-cause mortality and those who did not and for the three categories of albumin excretion were compared with the chi-square test; continuous variables were compared by analysis of variance or by the non-parametric Kruskal-Wallis test for non-normally distributed data.

Survival time was defined as the interval from urine collection to event or censoring, and averaged 2.9 [2.4-3.2] years. Unadjusted hazard ratios (HR) 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 three 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 less than 0.05 (age, sex, NYHA class, left ventricular ejection fraction (LVEF), etiology of HF, systolic and diastolic blood pressures (SBP, DBP), heart rate, prescription of ACE inhibitors, beta-blockers or diuretics, atrial fibrillation, chronic obstructive pulmonary disease (COPD) 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 two randomized treatments (n-3 PUFA vs. placebo and rosuvastatin vs. placebo) on urinary albumin excretion was evaluated in two ways. First, between-treatments differences in median UACR were compared with Wilcoxon’s rank sum test for the 2131 patients who gave a single urine sample during the study. Second, within-patients differences of absolute changes in UACR were compared separately for the two experimental arms in the 215 patients randomized to n-3 PUFA vs. placebo, and in the 143 randomized to rosuvastatin vs. placebo, whose urine samples were collected at randomization and after three months of follow-up, using rank ANCOVA (non-parametric analysis of covariance), controlling for the baseline value.

Statistical analysis was done using SAS software, version 9.1 (SAS Institute). 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 [1.5-30.9] mg/g creatinine (minimum 1.5, maximum 7867 mg/g, Table 1), 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 (≥ 300 mg/g). Patients with high albumin excretion were older, more frequently with a severe NYHA class, hypertension, diabetes or COPD (Table 1). They had higher heart rate, SBP and were prescribed beta-blockers less frequently and calcium antagonists more frequently. They had higher serum concentrations of creatinine and fibrinogen.

Figure 1 shows the relation between eGFR, an indicator of renal glomerular function, and urinary albumin excretion. The proportion of patients with impaired renal function (eGFR<60 mL/min/1.73 m²) was 30.1% in patients with normal urinary excretion, 45.0% in those with microalbuminuria and 53.0% in those with albuminuria (p<0.0001). There was a significant inverse linear relationship between the two continuous variables UACR and eGFR (Spearman coefficient of correlation \( r = -0.20 \), p<0.0001).
The prognostic value of urinary albumin excretion

In all, 428 patients died during the follow-up. Compared to 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 COPD was significantly more frequent among the patients who died. Beta-blockers were prescribed more to the survivors; the opposite was true for diuretics. Serum concentrations of creatinine, bilirubin and fibrinogen were higher in non-survivors. Median albumin excretion was significantly lower in survivors (7.6 [1.5-25.0] mg/g) than in those who died (15.8 [4.8-74.1] mg/g, p<0.0001). Similarly, albumin excretion was normal in more survivors (77.8 vs. 62.4%), whereas more of the patients with microalbuminuria (27.6 vs. 17.9%) or albuminuria (10.1 vs. 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, chi-square= 61, p<0.0001, Figure 2). Interestingly, the risk also increased within the “normal” albumin excretion ratio (0-30 mg/g): the unadjusted HR for mortality was significantly different from unity, starting from the sixth decile (UACR 15.3-23.1 mg/g) compared to the reference category (Figure 2).

Kaplan-Meier curves showed increasing mortality across the three categories of albumin excretion (log-rank test p<0.0001, Figure 3). Unadjusted mortality rates were respectively 16.8% (267 deaths/1592 patients at risk), 27.9% (118/423) and 37.1% (43/116) in patients with normal albumin excretion, microalbuminuria or albuminuria (Cochran-Armitage trend 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 [1.15-1.27] (HR [95%CI] per 1 unit increase of log(UACR), p<0.0001, Table 2). Compared to
patients with normal albumin excretion (n= 1592, referent), the risks of mortality were respectively
1.80 [1.45-2.24] and 2.48 [1.79-3.42] in those with microalbuminuria (n=423) and albuminuria
(n=116, p< 0.0001).

After adjusting for significant clinical risk factors reported at the time of urine collection,
UACR remained independently associated with mortality (HR [95%CI] = 1.12 [1.05-1.18] per 1 unit
increase of log(UACR), p=0.0002). This model included variables associated with diabetes (history
of diabetes), hypertension (SBP and DBP) and renal function (serum creatinine concentration).
Patients with microalbuminuria (HR [95%CI] = 1.42 [1.11-1.81]) and albuminuria (HR [95%CI]=
1.70 [1.16-2.50]) had a significantly higher risk of mortality than those with normal albumin
excretion, taken as the reference group (p= 0.005 and 0.006).

**Sex-specific cut-off values for albumin excretion**

The prognostic value of elevated albumin excretion was evaluated using sex-specific cut-off
values. In men, albumin excretion was considered normal if UACR was less than 17 mg/g,
microalbuminuria for UACR 17-249 mg/g and albuminuria for UACR greater than or equal to 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 three categories
of albumin excretion (log-rank test p<0.0001) and unadjusted mortality rates were respectively
16.0% (224 deaths/1401 patients at risk), 26.7% (162/606) and 33.9% (42/124) in patients with
normal albumin excretion, microalbuminuria or albuminuria (Cochran-Armitage test, p<0.0001). In
the adjusted Cox proportional hazard model, patients with microalbuminuria (HR [95%CI] = 1.36
[1.09-1.71]) and albuminuria (HR [95%CI]= 1.52 [1.02-2.25]) had a significantly higher risk of
mortality than those with normal albumin excretion, taken as the reference group (p= 0.04 and 0.008).

The prognostic role of urinary albumin excretion in patients without diabetes or hypertension

The prognostic value of urinary albumin excretion was assessed separately in the subgroup of 772 patients without diabetes or hypertension at study entry. Compared to the study population, these patients were slightly younger (65±11 vs. 67±11 years), were less frequently female (14.8 vs. 21.1%), or in NYHA classes III-IV (24.5 vs. 30.1%). The proportion of HF of ischemic etiology was lower (48.6 vs. 50.8%), and the mean LVEF slightly lower (32±8 vs. 33±9%, 93.7% of patients with LVEF≤0.40). Serum creatinine (1.10±1.04 vs. 1.18±0.40 mg/dL) and the proportion of patients with a low glomerular filtration rate (eGFR<60 mL/min/1.73 m²= 25.9 vs. 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 [5.4-98.0] mg/g, 29% with microalbuminuria, 12% with albuminuria) than in those without diabetes at enrolment (7.1 [1.4-21.4], 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 [1.5-38.4] mg/g, 22% with microalbuminuria, 6% with albuminuria) than in those without hypertension at enrolment (7.2 [1.4-22.9], p<0.0001; 17% with microalbuminuria, 4% with albuminuria).

Compared to 74.7% in the study population, 83.6% of the patients without diabetes or hypertension had normal excretion albumin rate, 13.6% were microalbuminuric, and 2.8% had albuminuria; median UACR was 6.15 [1.40-15.74] mg/g. In these patients, UACR was a univariate
predictor of mortality (HR [95%CI] = 1.21 [1.10-1.32] for an increase of one unit of log(UACR), p<0.0001, Table 2). After adjustment for risk factors, UACR remained weakly associated with mortality (1.10 [0.99-1.22] for an increase of one unit of log(UACR), p=0.08, Table 2).

**Effect of randomized treatments on urinary albumin excretion**

Among the patients who had a single collection of urine at any time during the trial (2131 in the n-3 PUFA arm, 1333 in the rosuvastatin arm), UACR was not significantly different in the n-3 PUFA arm (median UACR 8.66 mg/g for the active treatment and 8.79 mg/g for placebo, p=0.79) or in the rosuvastatin arm (median UACR 8.76 mg/g and 7.70 mg/g, p=0.34). In addition, there were no substantial differences in the changes in UACR between the 113 patients randomized to n-3 PUFA (baseline 6.64 [1.40-24.18], follow-up 6.98 [1.40-22.17] mg/g) and the 102 given placebo (baseline 9.12 [1.40-20.91], follow-up 9.92 [1.40-28.78] mg/g, rank ANCOVA p= 0.64) or between the 58 patients randomized to rosuvastatin (baseline 5.53 [1.40-20.91], follow-up 6.22 [1.40-24.33] mg/g) and the 85 given placebo (baseline 10.50 [1.40-36.33], follow-up 7.72 [1.40-28.78] mg/g, p= 0.33).
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 diabetics 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 change profoundly 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 (20,21). Two frequent comorbidities, hypertension and diabetes, are associated with renal dysfunction and generalized endothelial dysfunction which 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 (22). 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 (15-30 mg/g), as recently found (14). 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 (3,7,9). A gradual relationship between microalbuminuria and the incidence of venous thromboembolism has been found, even in the normal range of urinary albumin excretion (23). 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 diabetics) but probably encompass interplay with renal function (abnormalities of glomerular endothelial function) and more generalized endothelial dysfunction, a known risk factor for HF (9,10). The prevalence and prognostic value of albuminuria have also been investigated in patients with HF from the CHARM Programme (14). Although there are some differences in the demographic and clinical characteristics of the two populations (North American patients for CHARM, 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 two 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 (24). However, in the largest study (864 individuals from a general population in the city of Groningen, the Netherlands, median albuminuria 22-24 mg/24 h), pravastatin did not reduce albumin excretion (25). 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 (26). Urinary excretion of alpha1 microglobulin, but not albumin, also rises in a dose-dependent manner in hyperlipidemic patients treated with a statin (27). This indicated a reduction of protein reabsorption by the proximal tubular cells, as observed in isolated kidney cells (28).

In the present study, using daily dose of 10 mg of rosuvastatin, we saw no real differences in albumin excretion compared to placebo. In a recent trial, rosuvastatin did not improve outcome or renal function in patients undergoing maintenance hemodialysis (29). 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 (EPA, 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 (30). Three months of supplementation with n-3 PUFA (3.6 g daily, 57.4% EPA and 28.7% docosahexaenoic acid, DHA) marginally reduced absolute albumin excretion but not UACR in 24 patients with type 2 diabetes mellitus (31). 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 (18,19) or in clinical practice (32). 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 CHARM Programme (14).
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 (33), underestimate the number of patients with abnormal excretion of albumin (34) and affect its prediction of outcome (35). However, frozen urine samples are often used in large multicenter studies where albuminuria is determined by a central laboratory (24,36), 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 (37). Fifth, virtually all study participants were Caucasians 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 ACEi 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 endpoint for renoprotection (38). The patients enrolled in the GISSI-HF trial were intensively treated with drugs that should reduce urinary albumin excretion (93% were given an ACEi 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 utility of this marker for the management of patients with chronic HF.

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Legends to figures and tables

**Figure 1: Renal glomerular function and urinary albumin excretion**

The prevalence of classes of estimated glomerular function (eGFR) in the three categories of urinary albumin excretion was compared with the chi-square statistic ($p<0.0001$). The number of patients in each category is shown in the corresponding bar.

**Figure 2: Unadjusted hazard ratios and 95% confidence intervals for mortality by deciles of urinary albumin-to-creatinine ratio**

Unadjusted rate of mortality (HR [95%CI] for log(UACR)); 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; 152-160 patients per decile. Bars indicate the range of normal albumin excretion (green), microalbuminuria (MA, orange), and albuminuria (A, red). Chi-square=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 30-299 mg/g, $n=423$) or albuminuria (UACR$\geq300$ mg/g, $n=116$). Log-rank test, $p<0.0001$.

**Table 1: Baseline characteristics**

Patients’ baseline clinical characteristics according to albumin excretion. Continuous variables are expressed as mean±SD, except for UACR (median [Q1-Q3]).
Table 2: Multivariable Cox models for mortality in the study population and in the subgroup of patients without diabetes or hypertension at study entry

Hazard ratios for mortality are provided, with confidence intervals in square brackets, for the increments or categories specified.
Table 1

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<th>All patients</th>
<th>Urinary albumin excretion</th>
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<td>Ischemic HF (%)</td>
<td>50.8</td>
<td>51.1</td>
<td>48.7</td>
<td>53.5</td>
<td>0.57</td>
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<tr>
<td>LVEF (%)</td>
<td>33±9</td>
<td>33±8</td>
<td>34±10</td>
<td>33±8</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF&lt;0.40 (%)</td>
<td>90.8</td>
<td>91.6</td>
<td>88.2</td>
<td>88.8</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>71±14</td>
<td>71±14</td>
<td>74±14</td>
<td>72±13</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>127±18</td>
<td>126±18</td>
<td>129±19</td>
<td>134±16</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77±10</td>
<td>77±10</td>
<td>77±10</td>
<td>78±10</td>
<td>0.48</td>
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<tr>
<td>Hypertension (%)</td>
<td>55.5</td>
<td>53.1</td>
<td>61.9</td>
<td>64.7</td>
<td>0.0007</td>
<td></td>
<td></td>
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<tr>
<td>Diabetes (%)</td>
<td>26.1</td>
<td>20.5</td>
<td>38.1</td>
<td>58.6</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
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<tr>
<td>Atrial fibrillation (%)</td>
<td>19.5</td>
<td>18.7</td>
<td>22.5</td>
<td>19.0</td>
<td>0.22</td>
<td></td>
<td></td>
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<tr>
<td>COPD (%)</td>
<td>21.2</td>
<td>19.2</td>
<td>26.7</td>
<td>29.3</td>
<td>0.0003</td>
<td></td>
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<tr>
<td>ACEI or ARBs (%)</td>
<td>93.6</td>
<td>93.8</td>
<td>93.9</td>
<td>89.7</td>
<td>0.12</td>
<td></td>
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<tr>
<td>Beta-blockers (%)</td>
<td>67.9</td>
<td>69.9</td>
<td>62.2</td>
<td>60.3</td>
<td>&lt;0.0001</td>
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<tr>
<td>Diuretics (%)</td>
<td>88.6</td>
<td>87.1</td>
<td>93.1</td>
<td>93.1</td>
<td>0.0006</td>
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<tr>
<td>Calcium-antagonists (%)</td>
<td>10.6</td>
<td>8.9</td>
<td>13.5</td>
<td>24.1</td>
<td>&lt;0.0001</td>
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<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.18±0.40</td>
<td>1.14±0.33</td>
<td>1.26±0.51</td>
<td>1.44±0.61</td>
<td>&lt;0.0001</td>
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<tr>
<td>eGFR &lt;60 mL/min/1.73 m² (%)</td>
<td>35.7</td>
<td>30.1</td>
<td>45.0</td>
<td>53.0</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>0.82±0.64</td>
<td>0.82±0.67</td>
<td>0.85±0.59</td>
<td>0.76±0.43</td>
<td>0.09</td>
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<tr>
<td>Serum fibrinogen (mg/dL)</td>
<td>360±104</td>
<td>350±98</td>
<td>410±112</td>
<td>383±110</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
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<tr>
<td>Serum cholesterol (mg/dL)</td>
<td>192±43</td>
<td>193±42</td>
<td>190±43</td>
<td>186±51</td>
<td>0.20</td>
<td></td>
<td></td>
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<tr>
<td>Serum triglycerides (mg/dL)</td>
<td>146±101</td>
<td>146±104</td>
<td>146±82</td>
<td>155±116</td>
<td>0.69</td>
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</table>
### Table 2

<table>
<thead>
<tr>
<th>Variable (category or increment)</th>
<th>Study population (n=2131)</th>
<th></th>
<th>Patients without diabetes or hypertension (n=772)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR [95% CI]</td>
<td>p</td>
<td>HR [95% CI]</td>
<td>p</td>
</tr>
<tr>
<td><strong>Univariate model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Log (UACR) (1 unit)</td>
<td>1.21 [1.15-1.27]</td>
<td>&lt;0.0001</td>
<td>1.21 [1.10-1.32]</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Multivariable model</strong></td>
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<td></td>
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<tr>
<td>Log (UACR) (1 unit)</td>
<td>1.12 [1.05-1.18]</td>
<td>0.0002</td>
<td>1.10 [0.99-1.22]</td>
<td>0.08</td>
</tr>
<tr>
<td>Age (1 year)</td>
<td>1.04 [1.03-1.06]</td>
<td>&lt;0.0001</td>
<td>1.03 [1.01-1.05]</td>
<td>0.001</td>
</tr>
<tr>
<td>Beta-blockers (yes)</td>
<td>0.67 [0.53-0.83]</td>
<td>0.0003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log (serum creatinine) (1 unit)</td>
<td>2.16 [1.57-2.97]</td>
<td>&lt;0.0001</td>
<td>2.67 [1.98-5.95]</td>
<td>0.004</td>
</tr>
<tr>
<td>NYHA class (III-IV vs. II)</td>
<td>1.38 [1.10-1.74]</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (females)</td>
<td>0.72 [0.54-0.96]</td>
<td>0.03</td>
<td>0.47 [0.25-0.90]</td>
<td>0.02</td>
</tr>
<tr>
<td>Diuretics (yes)</td>
<td>1.80 [1.08-3.00]</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (1 bpm)</td>
<td>1.01 [1.00-1.02]</td>
<td>0.01</td>
<td>1.02 [1.00-1.03]</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Figure 1

![Figure 1: Bar chart showing the prevalence of eGFR (mL/min/1.73 m²) with different categories for normal, microalbuminuria, and albuminuria. The categories are ≥ 90, 60-90, 30-59, and <30. The chart indicates the number of cases in each category.]
Figure 2

All-cause mortality

Hazard ratio (95% CI)

Deciles

UACR (mg/g)
1.5-4.5
4.5-6.3
6.3-8.2
8.2-10.7
10.7-15.3
15.3-23.1
23.1-38.1
38.1-79.0
79.0-208.5
208.5-7867

Normal
MA
A
Figure 3

Log-rank test: p<0.0001

Probability of death

Normal
Microalbuminuria
Albuminuria

Number at risk
Normal 1592 1515 1375 728
Microalbuminuria 423 376 322 174
Albuminuria 116 98 83 51

Time (years)
Appendix - Participating centers and investigators

**Italy:** Acqui Terme (PL Roncarolo), Ascoli Piceno (L Moretti, G Gregori), Borgomanero (M Zanetta), Bovolone (S Boni), Cagliari (M Porcu), Casarano (G Pettinati, S Ciricugno), Castellamare di Stabia (L Caliendo), Catania (G Leonardi), Catanzaro (F Perticone), Chiari (D Raccagni), Città di Castello (D Severini), Cittadella (R Carlon), Cortona (F Cosmi, D Cosmi), Cosenza (G Misuraca), Cotignola (A Barbieri), Fidenza (E Buia), Firenze (C Minneci), Gallipoli (L Stella), Gazzaniga (C Malinverni), Genova, DIMI (A Pende), Genova-Sestri Ponente (D Caruso), Giussano (A Volpi, N Jones), Gubbio (M Buccolieri), Lagonegro (E Tagliamonte), Legnago (G Rigatelli, M Barbiero), Martina Franca (V Portulano), Mazara del Vallo (G Scillabra), Messina (G Di Tano), Milano Niguarda (L Beretta), Milano San Raffaele (A Margonato), Milazzo (C Coppolino), Mirano (P Sarto), Montescano (E Aiolfi), Mormanno (G Musca), Napoli (P Perrone Filardi), Negrar (P Girardi), Oliveto Citra (C Campaniello), Orbassano (P Greco Lucchina, L Montagna), Palermo, Cervello, Cardiologia I (G Geraci), Palermo, Cervello, Cardiologia II (M Floresta), Palermo, Villa Sofia (F Ingrilli), Passirana-Rho (A Frisinghelli, M Palvarini), Pavia, Salvatore Maugeri (C Opasich, A Gualco), Pavia, San Matteo (M Revera), Piedimonte Piemontese (R Battista, L De Risi), Pieve di Coriano (R Mazzucco), Portogruaro (D Milan), Reggio Calabria (A Ruggeri), Rimini (G Piovaccari), Rogliano (A Provenzano), Roma (A Varveri), San Bonifacio (E Carbonieri, I Rossi), San Daniele del Friuli (L Mos), Sondalo (N Partesana), Sondrio (G Cucchi), Soriano Calabro (L Anastasio), Terni (M Bernardinoangelii, G Proietti), Torino, Evangelico Valdese (N Massobrio), Torino, Maria Vittoria (M Imazio), Torino, Martini (R Fenoil), Torino, Gradenigo (S Gabasio), Trento (G Cioffi), Varese (I Ghezzi), Venosa (S Barbuzzi, S Gubelli), Veruno (P Giannuzzi, A Mezzani), Vigevano (G Graziano). **Switzerland:** Lugano (T Moccetti, MG Rossi).

**GISSI-HF Steering committee** - Luigi Tavazzi (Chairman), Gianni Tognoni (Co-Chairman), Maria Grazia Franzosi, Roberto Latin, Aldo P Maggioni, Roberto Marchioli, Gian Luigi Nicolosi, Maurizio
Porcu. Primary endpoint committee - Enrico Geraci (Chairman), Marino Scherillo (Co-Chairman), Gianna Fabbri (Coordinator), Barbara Bartolomei (Secretary), Daniele Bertoli, Franco Cobelli, Claudio Fresco, Antonietta Ledda, Giacomo Levantesi, Cristina Opasich, Franco Rusconi, Gianfranco Sinagra, Fabio Turazza, Alberto Volpi.
Prevalence and Prognostic Value of Elevated Urinary Albumin Excretion in Patients with Chronic Heart Failure. Data from the GISSI-Heart Failure (GISSI-HF) Trial
Serge Masson, Roberto Latini, Valentina Milani, Luciano Moretti, Maria Grazia Rossi, Emanuele Carbonieri, Anna Frisinghelli, Calogero Minneci, Massimiliano Valisi, Aldo P. Maggioni, Roberto Marchioli, Gianni Tognoni and Luigi Tavazzi

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