ORIGINAL RESEARCH

Prognostic Impact of Diabetes and Prediabetes on Survival Outcomes in Patients With Chronic Heart Failure: A Post-Hoc Analysis of the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure) Trial

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***Background*—**The independent prognostic impact of diabetes mellitus (DM) and prediabetes mellitus (pre-DM) on survival outcomes in patients with chronic heart failure has been investigated in observational registries and randomized, clinical trials, but the results have been often inconclusive or conflicting. We examined the independent prognostic impact of DM and pre-DM on survival outcomes in the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure) trial.

***Methods and Results*—**We assessed the risk of all-cause death and the composite of all-cause death or cardiovascular hospitalization over a median follow-up period of 3.9 years among the 6935 chronic heart failure participants of the GISSI-HF trial, who were stratified by presence of DM (n=2852), pre-DM (n=2013), and non-DM (n=2070) at baseline. Compared with non-DM patients, those with DM had remarkably higher incidence rates of all-cause death (34.5% versus 24.6%) and the composite end point (63.6% versus 54.7%). Conversely, both event rates were similar between non-DM patients and those with pre-DM. Cox regression analysis showed that DM, but not pre-DM, was associated with an increased risk of all-cause death (adjusted hazard ratio, 1.43; 95% CI, 1.28–1.60) and of the composite end point (adjusted hazard ratio, 1.23; 95% CI, 1.13–1.32), independently of established risk factors. In the DM subgroup, higher hemoglobin A1c was also independently associated with increased risk of both study outcomes (all-cause death: adjusted hazard ratio, 1.21; 95% CI, 1.02–1.43; and composite end point: adjusted hazard ratio, 1.14; 95% CI, 1.01–1.29, respectively).

***Conclusions*—**Presence of DM was independently associated with poor long-term survival outcomes in patients with chronic heart failure.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00336336. **(*J Am Heart Assoc*. 2017;6: e005156. DOI: 10.1161/JAHA.116.005156.)**

Key Words: chronic heart failure • diabetes mellitus • glycemic control • heart failure • mortality • prediabetes

Chronic heart failure (CHF) is a progressive, complex clinical syndrome characterized by considerably high rates of morbidity and mortality and results as a common aftermath of a wide range of cardiovascular damages, alone or in combination with other comorbid conditions, such as diabetes mellitus (DM), leading to early death.[1–6] The prevalence of DM in patients with heart failure (HF) is extremely high (occurring in up to 40–45% of these

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Clinical Perspective

What is New?

- Presently, there is intense debate about the independent prognostic impact of diabetes mellitus on the risk of long-term survival outcomes in patients with chronic heart failure.
- The added value of the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure) trial to existing literature is that it provides clear evidence on the independent prognostic role of diabetes mellitus on the risk of all-cause death and cardiovascular hospitalization in a cohort of nearly 6900 ambulatory patients with chronic heart failure followed-up for a median of 3.9 years.
- Another added value of the GISSI-HF trial is the finding of a significant association between elevated hemoglobin A1c levels and the risk of all-cause death and cardiovascular hospitalization among patients with diabetes mellitus, independent of multiple established risk factors.

What are the Clinical Implications?

- Collectively, these findings further reinforce the clinical importance for a more patient-centered, coordinated, and multidisciplinary team-based approach to the management of diabetes mellitus in patients with chronic heart failure.

patients).[7,8] Not surprisingly, the burden of morbidity and mortality associated with CHF and DM represents, to date, a major challenge for the prospective sustainability of contemporary healthcare systems.[8–11]

The most recent European Society of Cardiology guidelines have embraced the importance of a multidisciplinary team-based approach for the management of DM in patients with acute or CHF.[12] However, despite the existence of a significant association between hyperglycemia and adverse clinical outcomes in patients with HF,[9,13–15] no recommendations to identify specific glycemic goals or high-risk patient groups have been provided so far, mainly because of the lack of compelling evidence on the benefit of universally achieving a strict glycemic control.[16] Additionally, randomized, clinical trials that have explored the cardiovascular safety of the newer hypoglycemic drugs did not find any clear benefit on the risk of HF in patients with DM at high cardiovascular risk, except for opposite effects of empagliflozin (positive) and saxagliptin (negative) on the risk of HF hospitalization.[17–19]

Currently, there is intense debate about the independent prognostic impact of DM on the risk of long-term survival outcomes in patients with acute HF or CHF. For example, in a recent analysis of the Long-Term EURObservational Research Programme Heart Failure Registry, we found that the presence of DM was independently associated with an increased risk of in-hospital death, 1-year all-cause death, and 1-year HF re-hospitalizations in patients hospitalized for acute HF, thus supporting the importance of an early and appropriate management of DM in this patient population.[10] In contrast, Kosiborod et al did not find any significant association between the presence of pre-existing DM (or elevated glucose levels at hospital admission) and the risk of 30-day or 1-year mortality in a large, nationally representative cohort of US elderly patients hospitalized with HF.[20]

Notably, a number of other observational registries and randomized, clinical trials that explored the prognostic role of DM per se on survival outcomes in patients with HF have often reported inconclusive or conflicting results,[21–28] suggesting the need for further studies. In addition, very few studies also explored the independent prognostic role of pre-DM on survival outcomes in this particularly high-risk patient population. Clearly, these issues warrant further investigation.

Thus, in a post-hoc analysis of the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure) trial, we aimed at investigating whether the presence of DM and pre-DM independently affected the long-term survival outcomes in a large cohort of ambulatory patients with CHF.

Methods

Study Population and Design

The rationale and the study design of the GISSI-HF trial have been thoroughly presented elsewhere in previous publications,[29,30] and the registered study protocol is available online at https://clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT00336336).

Briefly, the GISSI-HF trial started in 2002 as a pragmatic, double-blind, placebo-controlled, nation-wide, multicenter study in 326 cardiology and 31 internal medicine centers with the specific aim of testing with a nested design the efficacy and safety of 2 different drugs (rosuvastatin 10 mg daily or n-3 polyunsaturated fatty acids [PUFAs] 1 g daily) in outpatients with CHF. Upon its completion in 2008, the trial enrolled 6975 patients aged ≥18 years with clinical evidence of HF of any cause that was classified according to the European Society of Cardiology guidelines as New York Heart Association (NYHA) functional class II to IV, provided that they had had their left ventricular ejection fraction (LVEF) measured within 3 months before the study enrollment. When LVEF was greater than 40%, the patient had to have been admitted to the hospital for HF at least once in the preceding year to meet the inclusion criteria.

Major exclusion criteria included: known hypersensitivity to the study treatments or ongoing treatment with the study drugs; presence of any noncardiac comorbidity that was unlikely to be compatible with sufficiently long follow-up (eg,

cancer); acute coronary syndrome or revascularization procedures within 1 month; planned cardiovascular surgery, expected to be performed within 3 months after randomization; significant liver diseases; serum creatinine concentrations >2.5 mg/dL; serum aminotransferase concentrations >1.5 times the upper normal limit; serum creatinine phosphokinase concentrations above the upper normal limit; and pregnant or lactating women or women of childbearing potential, who were not on contraceptive protection. The exact number of patients excluded for each condition was not systematically recorded in each participating center.

Two independent randomization schemes were then employed to test against placebo the effect of either n-3 PUFA or rosuvastatin on the occurrence of 2 co-primary prespecified study end points over a median follow-up period of 3.9 years: (1) all-cause death and (2) the composite of all-cause death or cardiovascular hospitalization. All study end points were adjudicated blindly by an ad-hoc committee on the basis of preagreed definitions and procedures. All reports included a narrative summary with supporting documentation for every event (eg, clinical records, death certificates, and any other relevant documentation).

The GISSI-HF trial was approved by each local institutional review board of all the participating centers. A written informed consent was obtained from each study participant before the study enrollment.

The primary results of the GISSI-HF trial have been already published and demonstrated a small beneficial advantage only by n-3 PUFA treatment, irrespective of pre-existing DM.[29,30]

The results herein presented pertain to a secondary analysis on 6935 participants (99.5% of total) from the GISSI-HF trial, who had available data on previous history of DM as well as fasting plasma glucose or hemoglobin A1c measurements at the study entry.

Diagnosis of DM, Pre-DM, and Other Clinical and Laboratory Data

According to widely accepted diagnostic criteria,[31,32] the presence of known or previously undiagnosed DM was defined as self-reported physician diagnosis of diabetes mellitus, current use of hypoglycemic drugs, a fasting plasma glucose level ≥7.0 mmol/L (≥126 mg/dL), or a hemoglobin A1c (HbA1c) level ≥6.5% (≥48 mmol/mol). Pre-DM was defined according to the presence of HbA1c from 6% (≥42 mmol/mol) to <6.5% (<47 mmol/mol) and/or fasting plasma glucose levels from 5.6 to 6.9 mmol/L (100–125 mg/dL). Patients without DM were defined as those without a previous history of DM and with a fasting plasma glucose level <5.6 mmol/L (<100 mg/dL) and HbA1c <6% (<42 mmol/mol).

Serum lipids, HbA1c, and other biochemical blood measurements were determined in all participants after an overnight fasting using standard laboratory procedures. The measurement of HbA1c was available for 5698 (82.2%) of 6935 patients. Body mass index was calculated by dividing patients' weight in kilograms by their height in squared meters. Patients were considered to have hypertension if their blood pressure was ≥140/90 mm Hg or if they were taking any antihypertensive drugs. The glomerular filtration rate was estimated by the 4-variable Modification of Diet in Renal Disease study equation.[33] The left ventricular diameter, wall thickness, and ejection fraction were assessed by conventional transthoracic echocardiography according to international standard criteria.

Statistical Analysis

Categorical variables are presented as percentages, whereas continuous variables are presented as means±SD. Categorical variables were compared by the chi-square test. The 1-way ANOVA was applied to compare all continuous variables across participants with different categories of glucose regulation, with the only exception of serum creatinine, glomerular filtration rate , and triglycerides, which were analyzed by the Kruskal–Wallis test, being not normally distributed. Multiple comparisons between patient groups (DM patients versus pre-DM patients; DM patients versus non-DM patients; and pre-DM patients versus non-DM patients) were also performed using the Bonferroni correction. Two multivariable Cox regression models (model 1: unadjusted; model 2: adjusted for age, sex, Body mass index, heart rate, systolic blood pressure, serum creatinine and cholesterol levels, smoking, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, NYHA functional class, HF etiology, and LVEF) were applied, with non-DM patients as the reference category, to estimate the risk that the presence of DM and pre-DM carried in terms of all-cause death and the composite end point inclusive of all-cause death or cardiovascular hospitalization. Covariates included in multivariable regression models were chosen as potential confounding factors on the basis of their significance in univariate regression analysis or on the basis of their biological plausibility. Because the risk of all-cause death or admission to hospital for cardiac reasons was affected by the study treatments (n-3 PUFAs or rosuvastatin) in all predefined subgroups in much the same way, with no evidence of heterogeneity of treatment effect,[29,30] we did not include the study treatment or placebo among the covariates. The same Cox regression models were also performed after excluding patients with baseline LVEF >40% from analysis.

In order to test whether a poorer quality of glycemic control at baseline was associated with a higher risk of adverse clinical outcomes over the follow-up period, we performed similar Cox regression analyses in the subgroup of

patients with available HbA1c measurements at baseline by simultaneously stratifying these patients according to their DM status and HbA1c tertiles. In order to obtain subgroups of comparable sample size, we separately examined the subgroup of patients with DM (n=2466) and the combined subgroup of patients with pre-DM and without DM (n=3232), by taking the first tertile of HbA1c within each subgroup as the reference category. Kaplan–Meier curves were also produced for both co-primary study end points and compared among the mentioned groups by the log-rank test.

Statistical significance was set at 2-sided *P* value of 0.05. All statistical tests were performed with SAS software (version 9.2; SAS Institute Inc, Cary, NC) at the GISSI-HF coordinating center (Florence, Italy).

Results

The study cohort comprised a total of 6935 (78.3% men) ambulatory patients with CHF. The age range was spanning from a minimum of 18 years to a maximum of 97 years, with a mean±SD of 67.2±11 years; around 42% of patients were older than 70 years. The mean LVEF of the entire cohort was 33.1±8%; 9.4% (n=652) of patients had a baseline LVEF >40%.

Prevalence of DM in the study cohort was high (n=2852; 41%); 69.2% (n=1974) of these patients had previously known DM (ie, self-reported history or use of hypoglycemic drugs), whereas the remaining 878 (30.8%) patients had previously undiagnosed DM. Among those with previously undiagnosed DM, 568 (64.7%) patients had an HbA1c ≥6.5% (of whom 151 also had a fasting glucose level ≥7.0 mmol/L), whereas the remaining 310 had a fasting glucose level ≥7.0 mmol/L (but with an HbA1c level <6.5%).

As shown in Table 1, compared with those with pre-DM or without DM, patients with DM were older (though the percentage of those aged ≥70 years was comparable among the three groups of patients), more likely to be female, had a higher number of comorbid conditions, such as obesity, hypertension, ischemic etiology of HF, chronic obstructive pulmonary disease, chronic kidney disease, and higher NYHA functional classes. Moreover, they also had (slightly) higher LVEF and were more likely to be treated with lipid-lowering and antiplatelet drugs, nitrates, digitalis, diuretics, aldosterone-antagonists, and calcium-channel blockers, but less often treated with amiodarone and beta-blockers. Randomized drug treatments started over the trial (n-3 PUFAs or rosuvastatin) were substantially comparable among the 3 groups of patients, except for a (slightly) lower percentage of non-DM patients randomized to rosuvastatin. Table 1 also shows *P* values for multiple comparisons between patient groups by using the Bonferroni correction.

Over the follow-up period of the trial (median duration, 3.9 years; interquartile range, 3.0–4.5 years), there were 1958 (28.2%) total deaths and 3302 (47.6%) patients admitted to the hospital because of cardiovascular reasons. The combined end point of all-cause death or cardiovascular hospitalization occurred in 4011 (57.8%) patients. Among the specific causes of death, 75.1% (n=1471) were cardiovascular (mainly attributed to worsening HF or sudden cardiac death), 21.1% (n=413) were noncardiovascular (mainly attributed to malignancy or acute infections), and 3.8% (n=74) were unknown. As shown in Table 2, no significant differences were found in the specific causes of death among patients stratified by their glycemic status at baseline (*P*=0.69).

As shown in Figure 1, patients with DM had remarkably higher (*P*<0.0001) cumulative incidence rates of all-cause death (n=984; 34.5%) compared with patients with pre-DM (n=465; 23.1%) or those without DM (n=509; 24.6%), respectively. The same applies to the co-primary outcome of all-cause death or cardiovascular hospitalization: Of 4011 (57.8%) patients with the combined end point over the follow-up, the event rates were higher in patients with DM (n=1814; 63.6%) than in those with pre-DM (n=1064; 52.9%) and in those without DM (n=1133; 54.7%). Moreover, patients with DM also had significantly higher rates of cardiovascular hospitalization alone (n=1481; 51.9%) compared with those with pre-DM (n=887; 44.1%) and those without DM (n=934; 45.1%), respectively.

The visual inspection of the Kaplan–Meier curves for the rates of all-cause death (Figure 2), and the composite of all-cause death or cardiovascular hospitalization (Figure 3) shows the data just reported, also substantially higher incidence rates of both clinical end points in patients with DM compared with pre-DM and non-DM patients over the follow-up period (*P*<0.0001, by the log-rank test). Conversely, no significant differences in these clinical outcomes were found between patients with pre-DM and those without DM.

Table 3 shows that patients with DM had an ≈1.5-fold increased risk of all-cause death and a 1.3-fold increased risk for the composite of all-cause death or cardiovascular hospitalization compared with patients without DM. The robustness of these associations did hold in Cox regression analysis even after adjustment for multiple clinical risk factors and potential confounding variables, with an adjusted hazard ratio of 1.43 (95% CI, 1.28–1.60; *P*<0.0001) for all-cause death and 1.23 (95% CI, 1.13–1.32; *P*<0.0001) for the composite end point, respectively. Among the covariates included in the fully adjusted regression model, the following also showed an independent association with the risk of both clinical end points: older age, lower body mass index, lower systolic blood pressure, lower total cholesterol, higher serum creatinine, presence of atrial fibrillation/flutter, previous chronic obstructive pulmonary disease, ischemic etiology of HF, higher NYHA functional class, and lower LVEF. Almost identical results were found when the study treatments (n-3

Table 1. Baseline Clinical and Biochemical Characteristics of Patients With Chronic HF Enrolled in the GISSI-HF Trial, Stratified by Glycemic Status at Baseline

	DM Patients (n=2852)	Pre-DM Patients (n=2013)	Non-DM Patients (n=2070)	*P* Value
Males, %	77*	81	78	<0.01†
Age, y	68±10*	67±11	66±12‡	<0.0001†
Age ≥70 y, %	43	42	42	0.90
NYHA class, III to IV, %	42*	33	33‡	<0.0001†
BMI, kg/m^2	28±5*	27±4§	26±4‡	<0.0001†
BMI ≥30 kg/m^2, %	29*	21§	15‡	<0.0001†
Systolic blood pressure, mm Hg	128±18*	126±17§	124±18‡	<0.0001†
Diastolic blood pressure, mm Hg	77±10	77±10	76±10‡	<0.01†
Heart rate, bpm	74±13*	72±13	71±13‡	<0.001†
Diabetes mellitus treatment at randomization, %				
Insulin	19	…	…	NA
Oral drugs only	39	…	…	NA
Diet only	42	…	…	NA
Hemoglobin, g/dL	13.6±1.7*	13.9±1.6§	13.7±1.6‡	<0.0001†
Total cholesterol, mg/dL	188±44*	195±43§	191±41‡	<0.0001†
Triglycerides, mg/dL	161±104*	142±87§	131±79‡	<0.0001†
Fasting glucose, mmol/L	8.33±3.2*	5.83±0.6§	4.89±0.4‡	<0.0001†
Hemoglobin A1c, %‖	7.2±1.6*	5.7±0.6§	5.2±0.6‡	<0.0001†
Hypertension, %	63*	52§	46‡	<0.0001†
Current smoking, %	13	15	15	0.061
Lipid-lowering medications at randomization, %	25	23	20‡	<0.001†
Cardiovascular medications at randomization, %				
ACE-I or ARBs	94	93	94	0.15
Beta-blockers	62*	67	66	0.001†
Aldosterone-antagonists	42	40§	36‡	<0.001†
Diuretics	93*	88	87‡	<0.001†
Digitalis	39*	35	36	0.01†
CCBs	13*	9	8‡	<0.0001†
Antiplatelets	60*	54	54‡	<0.0001†
Anticoagulants	28	30	29	0.60
Nitrates	40*	33	32‡	<0.0001†
Amiodarone	18	20	22‡	<0.001†
Randomized drug treatment, %				
n-3 PUFAs	50	50	51	0.91
Rosuvastatin¶	52	50	47‡	0.03†
Creatinine, mg/dL	1.3±0.5*	1.2±0.5§	1.2±0.4‡	<0.0001†
eGFR$_{MDRD}$, mL/min per 1.73 m^2	65.6±24.9*	69.3±21.6	70.6±22.3‡	<0.0001†
LVEF, %	33.3±8.6	33.2±8.5	32.7±8.3‡	0.03†
LVEF >40%, %	11	9	8‡	<0.01†
HF etiology, ischemic, %	56*	46	45‡	<0.0001†
Atrial fibrillation/flutter, %	17	17	15	0.07

Continued

Table 1. Continued

	DM Patients (n=2852)	Pre-DM Patients (n=2013)	Non-DM Patients (n=2070)	*P* Value
COPD, %	25*	21	19‡	<0.0001†
Previous neoplasm, %	3	4	4	0.35
Pacemaker, %	13	13	12	0.60
Previous ICD, %	6	7	9‡	0.014†
Previous IHD, %	52*	44	42‡	<0.0001†
Previous stroke, %	6	5	4‡	<0.005†

Cohort size, n=6935, data presented as means±SD or percentages. One-way ANOVA was applied to all continuous variables with the only exception of serum creatinine, triglycerides, and eGFR, which were analyzed by the Kruskal–Wallis test. ARBs indicates angiotensin receptor blockers; BMI, body mass index; CCBs, calcium-channel blockers; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; $eGFR_{MDRD}$, glomerular filtration rate estimated according to the Modification of Diet in Renal Disease (MDRD) study equation; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure; HF, heart failure; ICD, implantable cardioverter defibrillator; IHD, ischemic heart disease (ie, composite end point of myocardial infarction or angina pectoris); LVEF, left ventricular ejection fraction; NA, not applicable; NYHA, New York Heart Association; PUFAs, polyunsaturated fatty acids.
*P<0.017 for comparison between DM patients and pre-DM patients (by the Bonferroni correction).
†Two-tailed P<0.05 for comparison among DM patients, pre-DM patients and non-DM patients (1-way ANOVA or Kruskal-Wallis).
‡P<0.017 for comparison between DM patients and non-DM patients (by the Bonferroni correction).
§P<0.017 for comparison between pre-DM patients and non-DM patients (by the Bonferroni correction).
‖Hemoglobin A1c measurements were available for n=5698 patients.
¶Percentages evaluated on 4546 patients randomized to rosuvastatin/placebo.

PUFAs or rosuvastatin) were included as additional covariates in these multivariable regression models; in all models, the adjusted hazard ratios for both pre-DM status and DM status remained unchanged. Moreover, both study treatments were not significantly associated with the risk of all-cause death and the composite of all-cause death or cardiovascular hospitalization in any of these regression models (data not shown).

Table 4 shows the results of Cox regression analysis of all-cause death alone or in combination with cardiovascular hospitalization in patients with CHF after excluding those with LVEF >40% at the study entry (n=652). Also in this case, the results remained essentially unchanged showing that the presence of DM, but not pre-DM, was significantly associated with an increased risk of all-cause death and of the composite end point after adjusting for potential confounding variables.

Table 2. Specific Causes of Death in Patients With Chronic HF Enrolled in the GISSI-HF Trial, Who Were Stratified by Their Glycemic Status at Baseline (ie, Patients With DM, Patients With Pre-DM, and Those Without Diabetes Mellitus [Non-DM], Respectively)

Causes of Death	No. of Died Patients With DM (n=984)	No. of Died Patients With Pre-DM (n=465)	No. of Died Patients Without DM (n=509)
Cardiovascular	742 (75.4%)	356 (76.6%)	373 (73.3%)
Noncardiovascular	202 (20.5%)	93 (20.0%)	118 (23.2%)
Unknown	40 (4.1%)	16 (3.4%)	18 (3.5%)

GISSI-HF indicates Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure; HF, heart failure.

Table 5 shows the change in the risk of study outcomes across worsening classes of glycemic control in the subgroup of CHF patients (n=5698) with available HbA1c measurements at baseline. Compared with the combined group of pre-DM and non-DM patients, those with DM had always higher rates per 100 patient-years for both study outcomes at each level of HbA1c. In particular, the event rates of all-cause death across HbA1c tertiles were almost double in patients with DM compared with those in the combined group of pre-DM and non-DM patients. Moreover, in the DM group, the association between glycemic control and the risk of clinical outcomes was statistically significant in the third tertile of HbA1c (HbA1c >7.5%) after adjustment for multiple potential confounding variables, with an adjusted hazard ratio of 1.21 (95% CI, 1.02–1.43) for all-cause death and 1.14 (95% CI, 1.01–1.29) for the combined end point, respectively.

Discussion

The main findings of this post-hoc analysis of the GISSI-HF trial are as follows: (1) pre-DM and DM were 2 extremely common pathologic conditions in ambulatory patients with CHF (29% and 41%, respectively); (2) the presence of known or previously undiagnosed DM was significantly associated with a higher risk of both all-cause death or cardiovascular hospitalization, whereas the presence of pre-DM was not; (3) the association between DM and the risk of long-term clinical outcomes remained significant even after adjustment for multiple established risk factors and potential confounding variables; and (4) in patients with DM, the risk of long-term clinical outcomes was independently associated with poor glycemic control (as measured by HbA1c levels).

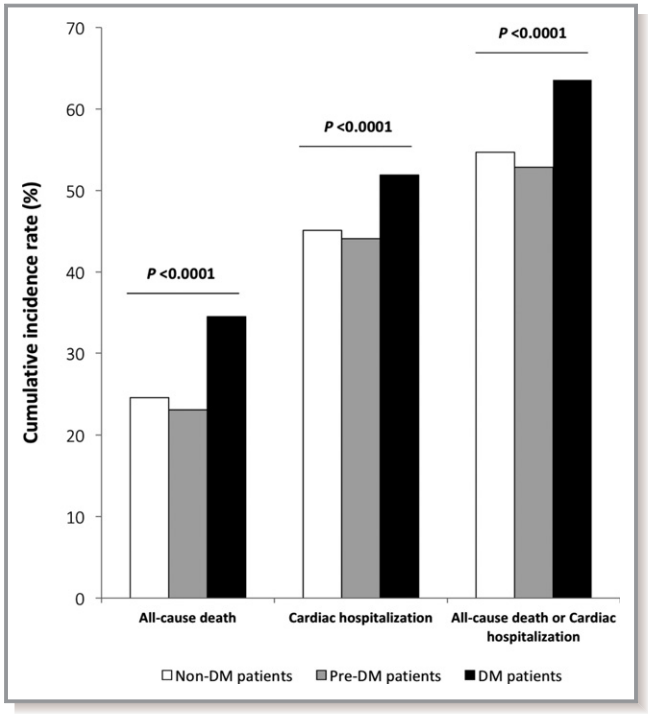

Figure 1. Cumulative incidence rates of all-cause death and cardiovascular hospitalization in patients with chronic heart failure from the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure) trial, who were stratified by baseline glycemic status. The panel shows the occurrence of all-cause death and cardiovascular hospitalization, singly or in combination, in patients with diabetes mellitus (DM; n=2852), patients with prediabetes mellitus (pre-DM; n=2013), and those without diabetes mellitus (non-DM; n=2070), who were followed-up for a median of 3.9 years.

The independent prognostic impact of DM on survival outcomes in patients with CHF has been investigated in observational registries and randomized, clinical trials, but the results have been often inconclusive or conflicting.[4,9,20–24,27,28,34] Similarly, few studies have investigated the prevalence of pre-DM in patients with CHF and even fewer its clinical consequences (and with conflicting findings).[9,14,20,24]

In particular, the results of the GISSI-HF trial contrast with those from other previously published clinical trials, including the SOLVD (Studies Of Left Ventricular Dysfunction) Prevention and Treatment trial, the DIG (Digitalis Investigation Group) trial, and the BEST (Beta-Blocker Evaluation of Survival) trial,[21–23] which have reported that the independent prognostic impact of DM, if any, on survival outcomes in patients with advanced HF might be confined only to those with ischemic cardiomyopathy. The OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with HF) registry also showed that patients with coexistent HF and DM had similar rates of in-hospital and 3-month postdischarge survival outcomes compared with those without DM.[27] Moreover, Kosiborod et al did not find any significant association between DM and 1-year all-cause mortality in a nationally representative cohort of 50 532 US elderly patients hospitalized with HF.[20] More recently, in the IN-HF (Italian Network on Heart Failure) Outcome registry cohort of nearly 1800 patients hospitalized with acute HF, we found that patients with previously known DM had significantly higher in-hospital death rates, but similar postdischarge 1-year death rates compared with those without DM.[26]

However, the findings of the GISSI-HF trial confirm and extend the results of other large, randomized, clinical trials, supporting the existence of a significant and independent association between DM and poor long-term clinical outcomes in patients with CHF. For instance, the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) trial, involving nearly 7600 patients with symptomatic CHF who were followed-up for a median period of ≈3 years, reported that pre-existing DM was a powerful predictor of all-cause death and of a composite of cardiovascular death or HF hospitalization.[34] Furthermore, a meta-analysis of 30 cohort studies (6 of which were randomized, clinical trials) that included individual data on nearly 39 000 patients with CHF has shown that the presence of DM predicted independently the risk of all-cause death over a median follow-up period of 2.5 years.[4] Recently, a post-hoc analysis of the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial reported that both DM and pre-DM were independently associated with an increased risk of the composite of cardiovascular death or HF hospitalization in 8399 CHF patients with LVEF <35%, who were randomly assigned to sacubutril/valsartan treatment or enalapril and followed-up for 3 years.[24]

Interestingly, in agreement with some previous studies,[34,35] we found that having a diagnosis of DM, a worsening of NYHA class and a previous history of chronic obstructive pulmonary disease each accounted by a comparable order of magnitude for the higher long-term risk of all-cause death or cardiovascular hospitalization observed in patients with HF.

In contrast to the findings of the PARADIGM-HF trial, in this study we did not find a mortality risk continuum across the entire range of glucose regulation categories, given that patients with pre-DM did not show significantly higher incidence rates of all-cause death or cardiovascular hospitalization compared with those without DM over the follow-up. This might be partly attributed to differences both in the study design and in the clinical characteristics of patients enrolled in the GISSI-HF trial (which was essentially a pragmatic, all-comer–oriented clinical trial) and in the PARADIGM-HF trial (which adopted very strict enrollment criteria, including the presence of LVEF <35% and the study drug tolerability in a long run-in observational period). However, our findings are also consistent with those reported by Goode et al,[14] who did not observe any significant increase in the risk of all-cause

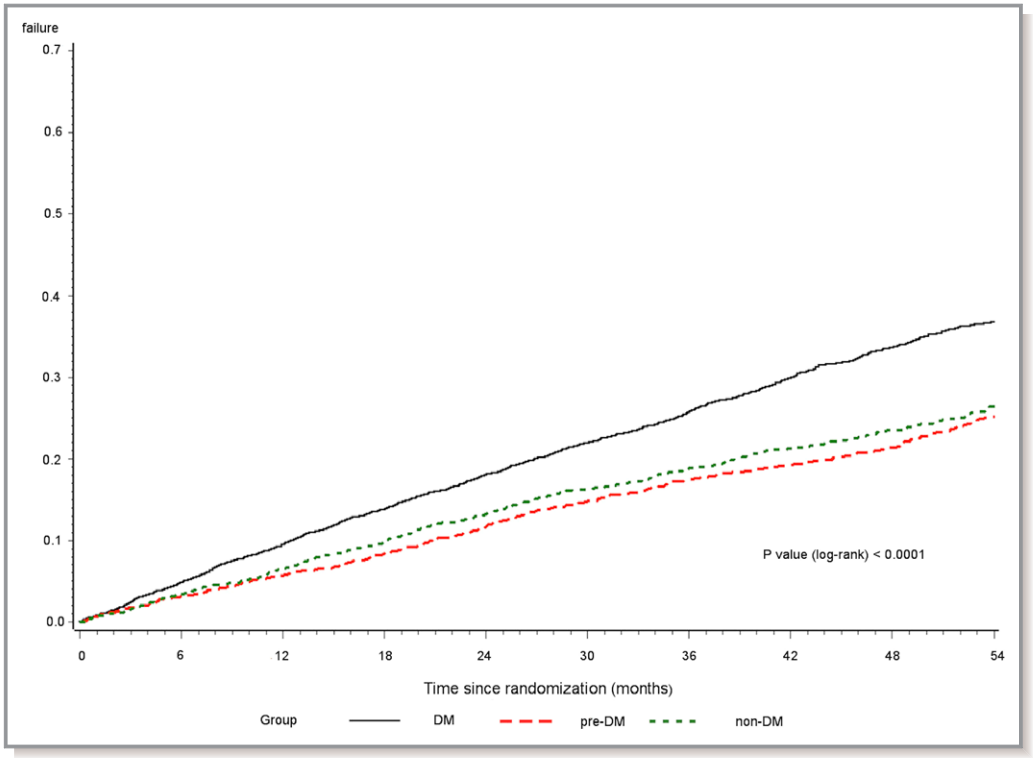

Figure 2. Kaplan–Meier curves for time to all-cause death among the 3 groups of patients with chronic heart failure, who were stratified by baseline glycemic status.

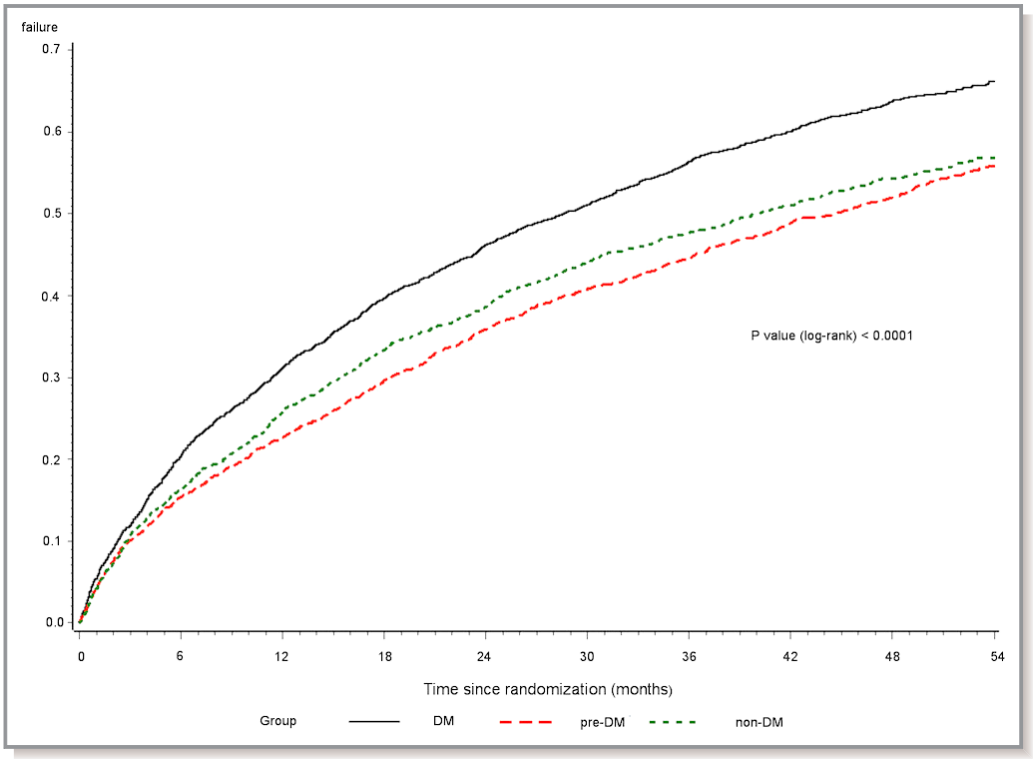

Figure 3. Kaplan–Meier curves for time to all-cause death or cardiovascular hospitalization among the 3 groups of patients with chronic heart failure, who were stratified by baseline glycemic status. DM indicates diabetes mellitus.

Table 3. Cox Regression Analysis of All-Cause Death Alone or in Combination With Cardiovascular Hospitalization in the Whole Cohort of Patients With Chronic HF Enrolled in the GISSI-HF Trial

	All-Cause Death		All-Cause Death or Cardiovascular Hospitalization (Combined End Point)	
Variables	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR
Non-DM	Ref.	Ref.	Ref.	Ref.
Pre-DM status (yes vs no)	0.93 [0.82–1.05]	0.93 [0.82–1.06]	0.94 [0.86–1.02]	0.94 [0.86–1.02]
DM status (yes vs no)	1.50 [1.35–1.67]*	1.43 [1.28–1.60]*	1.28 [1.19–1.38]*	1.23 [1.13–1.32]*
Sex (female vs male)	…	0.82 [0.73–0.93]*	…	0.93 [0.86–1.01]
NYHA functional class (III–IV vs I–II)	…	1.53 [1.39–1.68]*	…	1.33 [1.25–1.43]*
Age, y	…	1.05 [1.04–1.05]*	…	1.02 [1.01–1.03]*
Systolic blood pressure, mm Hg	…	0.99 [0.989–0.995]*	…	0.99 [0.990–0.994]*
Heart rate, bpm	…	1.01 [1.003–1.009]*	…	1.00 [0.999–1.003]
BMI, kg/m^2	…	0.97 [0.96–0.98]*	…	0.99 [0.98–0.99]*
Smoking (yes vs no)	…	0.96 [0.82–1.11]	…	0.96 [0.87–1.06]
Hypertension (yes vs no)	…	0.90 [0.82–0.99]*	…	1.01 [0.95–1.08]
Atrial fibrillation/flutter (yes vs no)	…	1.21 [1.09–1.33]*	…	1.25 [1.17–1.34]*
COPD (yes vs no)	…	1.43 [1.30–1.58]*	…	1.24 [1.15–1.34]*
HF etiology (ischemic vs nonischemic)	…	1.22 [1.11–1.34]*	…	1.28 [1.20–1.37]*
LVEF (%)	…	0.98 [0.978–0.989]*	…	0.98 [0.978–0.986]*
Total cholesterol, mg/dL	…	0.99 [0.997–0.999]*	…	0.99 [0.998–1.000]*
Creatinine, mg/dL	…	1.34 [1.27–1.40]*	…	1.22 [1.17–1.27]*

Cohort size, n=6935; data are expressed as HR and 95% CI (in parenthesis). Ref., reference category. Continuous variables were included in the multivariable regression model as continuous measures. BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
*Significant ($P < 0.05$) associations.

death among nondiabetic CHF patients with a HbA1c level less than 6.5%.

Collectively, we believe that the added value of the GISSI-HF trial to existing literature is that it provides clear evidence on the prognostic role of DM per se on the risk of long-term survival outcomes in a large cohort of outpatients with CHF. Although clinical trial databases, like this, have limitations of being selective compared with general practice, they provide the advantage of systematic data collection and complete high-quality follow-up. Moreover, all study outcomes of the GISSI-HF trial were prospectively collected and blindly adjudicated.

Another added value of the GISSI-HF trial is the finding of a significant association between poor glycemic control (as measured by HbA1c level that was available in most of our patients at baseline) and the risk of all-cause death and cardiovascular hospitalization in patients with DM, independent of multiple clinical risk factors and potential confounders. Therefore, our findings further reinforce the clinical importance for a patient-centered, team-based approach to the management of patients with coexistent HF and DM.

However, our study has some important limitations that should be kept in mind: (1) As mentioned previously, this is a post-hoc analysis of the GISSI-HF trial that was not primarily undertaken to examine the prognostic impact of DM and pre-DM on long-term survival outcomes of patients with CHF; (2) despite that both fasting plasma glucose and HbA1c levels were available for the majority of the GISSI-HF participants, the diagnosis of newly diagnosed DM was based on HbA1c and/or with a single-point fasting glucose measurement, without further systematic confirmation by a second determination on a separate day; however, this is an intrinsic limitation of all large, observational registries and randomized, clinical trials, in which the confirmation of DM diagnosis, on at least 2 separate occasions, in patients with newly diagnosed DM has been never made; (3) the GISSI-HF participants were not necessarily representative of the garden variety of ambulatory patients with CHF, because the results herein presented pertain to a population of outpatients with CHF, mainly followed by cardiologists and specifically selected to be enrolled in a clinical trial; and (4) detailed information about the presence of obstructive sleep apnea, duration of diabetes mellitus, use of different classes of oral hypoglycemic agents as well as follow-up data on fasting glucose and HbA1c measurements were not available.

Table 4. Cox Regression Analysis of All-Cause Death Alone or in Combination With Cardiovascular Hospitalization in Patients With Chronic HF and LVEF ≤40% Enrolled in the GISSI-HF Trial

	All-Cause Death		All-Cause Death or Cardiovascular Hospitalization (Combined End Point)	
Variables	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR
Non-DM	Ref.	Ref.	Ref.	Ref.
Pre-DM status (yes vs no)	0.91 [0.80–1.04]	0.93 [0.82–1.07]	0.91 [0.84–1.00]*	0.93 [0.85–1.01]
DM status (yes vs no)	1.54 [1.37–1.72]*	1.45 [1.29–1.62]*	1.26 [1.17–1.36]*	1.21 [1.11–1.31]*
Sex (female vs male)	…	0.79 [0.69–0.90]*	…	0.90 [0.82–0.99]
NYHA functional class (III–IV vs I–II)	…	1.47 [1.33–1.63]*	…	1.28 [1.19–1.38]*
Age, y	…	1.04 [1.036–1.048]*	…	1.01 [1.009–1.016]*
Systolic blood pressure, mm Hg	…	0.99 [0.989–0.995]*	…	0.99 [0.990–0.994]*
Heart rate, bpm	…	1.01 [1.002–1.009]*	…	1.00 [0.999–1.004]
BMI, kg/m^2	…	0.97 [0.96–0.98]*	…	0.99 [0.981–0.997]*
Smoking (yes vs no)	…	0.95 [0.82–1.11]	…	0.97 [0.88–1.07]
Hypertension (yes vs no)	…	0.92 [0.83–1.01]	…	1.01 [0.94–1.09]
Atrial fibrillation/flutter (yes vs no)	…	1.20 [1.08–1.33]*	…	1.24 [1.15–1.33]*
COPD (yes vs no)	…	1.43 [1.28–1.59]*	…	1.24 [1.14–1.34]*
HF etiology (ischemic vs nonischemic)	…	1.26 [1.14–1.39]*	…	1.33 [1.25–1.43]*
LVEF (%)	…	0.97 [0.962–0.977]*	…	0.97 [0.962–0.972]*
Total cholesterol, mg/dL	…	0.99 [0.997–0.999]*	…	0.99 [0.998–1.000]*
Creatinine, mg/dL	…	1.33 [1.26–1.40]*	…	1.22 [1.17–1.28]*

Cohort size, n=6283; data are expressed as HR and 95% CI (in parenthesis). Ref., reference category. Continuous variables were included in the multivariable regression model as continuous measures. BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; GISSI-HF indicates Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
*Significant ($P < 0.05$) associations.

Table 5. Association Between HbA1c Tertiles at Baseline and Adverse Clinical Outcomes in a Subset of Patients With Chronic HF Who Had Available HbA1c Measurements

Subgroup(s)	Clinical Outcome(s)	HbA1c Tertiles (%)	Events/ Patients	Rate Per 100 Patient-Years [95% CI]	Adjusted* HR [95% CI]
Patients with DM (n=2466)	All-cause death	≤6.5	288/844	10.0 [8.9–11.2]	Ref.
		6.6 to 7.5	269/820	9.6 [8.5–10.8]	0.96 [0.81–1.14]
		>7.5	286/802	10.6 [9.4–11.8]	1.21 [1.02–1.43]*
	Combined end point	≤6.5	525/844	18.2 [16.7–19.8]	Ref.
		6.6 to 7.5	517/820	18.4 [16.9–20.0]	0.99 [0.88–1.12]
		>7.5	521/802	19.2 [17.7–21.0]	1.14 [1.01–1.29]*
Patients with Pre-DM or non-DM (n=3232)	All-cause death	≤5.3	237/1102	5.7 [5.0–6.5]	Ref.
		5.4 to 5.8	272/1135	6.6 [5.8–7.4]	1.09 [0.92–1.30]
		>5.8	248/995	7.0 [6.2–7.9]	1.07 [0.90–1.29]
	Combined end point	≤5.3	557/1102	13.4 [12.3–14.5]	Ref.
		5.4 to 5.8	601/1135	14.5 [13.4–15.7]	1.04 [0.93–1.17]
		>5.8	562/995	15.9 [14.6–17.2]	1.10 [0.98–1.24]

Cohort size, n=5698 with available HbA1c measurements at baseline. Ref., reference category. In this analysis, patients with non-DM and pre-DM were combined into a single group. DM indicates diabetes mellitus; HbA1c, hemoglobin A1c; HF, heart failure; HR, hazard ratio.
*Covariates for adjustment are the same of those reported in Table 3: sex, age, body mass index, heart rate, New York Heart Association functional class, systolic blood pressure, smoking, hypertension, atrial fibrillation/flutter, chronic obstructive pulmonary disorder, ischemic heart failure etiology, left ventricular ejection fraction, serum total cholesterol, and creatinine levels.
*Significant ($P < 0.05$) associations.

In conclusion, the results of the GISSI-HF trial show that the presence of known or previously undiagnosed DM was independently associated with an increased risk of all-cause death and cardiovascular hospitalization in ambulatory patients with CHF over a median follow-up period of 3.9 years. Conversely, the rates of both clinical outcomes were similar between patients with pre-DM and those without DM. In an era in which there is increasing emphasis on chronic disease preventive care as a strategy to contain healthcare costs, our results further highlight the prognostic value of DM and the need for therapies that improve survival outcomes in patients with coexistent CHF and DM. As also anticipated by the 2016 European Society of Cardiology guidelines,[12] the optimization of the individual treatment for DM and other accompanying modifiable cardiovascular risk factors in patients with HF needs a mindset change, from a less "cardiocentric" approach to a more-comprehensive clinical care in a multidisciplinary HF team.

Appendix

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Author Contributions

Targher, Tavazzi and Maggioni conceived and designed the study. Dauriz and Targher wrote the manuscript draft. Lucci and Gonzini analyzed the data. Temporelli, Nicolosi, Marchioli, Tognoni, Latini, Cosmi, Tavazzi, and Maggioni researched the data, contributed to discussion, and reviewed/edited the manuscript. All authors read and approved the final version of the manuscript. Maggioni is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data.

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Disclosures

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