Modes of death and prognostic outliers in chronic heart failure

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Background The impact of incident sudden cardiac death (SCD) on the predictive accuracy of prognostic risk scores for patients with chronic heart failure (HF) has rarely been examined. We assessed the relationship between estimated probability of death and modes of death in this population, as well as the predictors of death and survival in prognostic outliers.

Methods and Results The MAGGIC 3-year probability of death was estimated in 6,859 participants of the GISSI-HF trial (mean age 67±11 years, 78% men, 91% with ejection fraction <40%, mean follow-up 3.5±1.3 years, observed mortality 28.4%). The incidence of SCD progressively decreased with increased probability of death, and occurred in 52.5% of patients estimated at low-risk (N = 61 with probability <14%) vs. in 23.5% of the high-risk ones (N = 375 with probability >56%, $P < .0001$). On the contrary, death from worsening HF was significantly more frequent in the latter group (19.7% vs. 46.1%, $P < .0001$). The overall predictive accuracy of the MAGGIC model improved after excluding deaths from SCD (AUC from 0.731 to 0.760, $P = .0034$). Among patients estimated at low-risk (N = 61 dead, 743 alive), independent predictors of death were older age, longer history of HF, higher serum uric acid and chronic obstructive pulmonary disease. The only predictor of survival in patients estimated at high-risk (N = 210 alive, 375 dead) was higher systolic blood pressure.

Conclusions The MAGGIC risk score demonstrated its scarce ability to capture SCD, particularly in chronic HF patients estimated at low risk of death. Newer and better prognostic tools in the evolving horizon of HF are needed. (Am Heart J 2019;208:100-9.)

Patients with chronic heart failure (HF) experience a disproportionate number of events during their lifetime, and death primarily occurs for cardiovascular reasons, especially in HF patients with reduced ejection fraction (HFrEF).[1] Although overwhelming evidences demonstrated that ventricular arrhythmias are prevalent and account for the majority of sudden cardiac death (SCD) in ambulatory patients with HFrEF,[2] the implementation of triple neurohumoral blockade therapy has determined a significant decline in the rate of sudden death over time in this population,[3] with an annual rate of 3.3% in the most recent trial.[4] In addition, HF with preserved left ventricular ejection fraction (HFpEF) is increasingly diagnosed, and today accounts for approximately half of prevalent HF, and this proportion is expected to rise with aging of the population.[5] SCD justifies about 40% of all-cause mortality in HFrEF patients versus about 25% in HFpEF ones, who seem to die more frequently of non-cardiovascular causes.[1] However, the absolute number of SCD is actually much higher among subjects with HFpEF or only moderately reduced left ventricular ejection fraction (HFmrEF), who are judged to be at lower risk if only LV function is considered.[6] Thus, the whole HF prognostic scenario is rapidly evolving, with SCD being one unexpected event among multiple competing ones during the course of the HF disease.

Several prognostic risk scores mainly focused on HFrEF patients have been developed in the past two decades.[7] By incorporating parameters from multiple domains, they have been primarily designed to estimate probability of all-cause mortality at 1-to-5 year follow-up,[8] with a

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discrimination capacity in validation cohorts estimated between 0.63 and 0.81.[7] However, the impact of incident SCD on this imperfect predictive accuracy has rarely been investigated. A single analysis of data from 6 HF randomized trials and registries conducted before the year 2000 has shown that unexpected deaths in HFrEF patients estimated to be at low risk of death by the Seattle Heart Failure Model (SHFM) prognostic score occurred primarily because of sudden death.[9] More recently, the MAGGIC score obtained from a database of more than 39,000 HF patients has been proposed,[10] and demonstrated to have a significantly better accuracy than the SHFM in predicting all-cause mortality.[8] However, its performance according to different modes of deaths in the HFrEF population, although presumably important,[11] has never been investigated. A thorough analysis of individual-patient prognostic estimations and of "prognostic outliers" (i.e. patients unexpectedly dead despite being estimated at low risk, and the opposite) could help unraveling major issues in the MAGGIC risk score, and enhance its use by cardiologists in daily clinical practice.[8]

Using data from patients with chronic HF enrolled in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca–Heart Failure (GISSI-HF) study,[12] we assessed i) the relationship between probability of death estimated using the MAGGIC risk score and modes of death, ii) the characteristics and modes of death of prognostic outliers, and iii) the predictors of death and survival in patients estimated to be respectively at low-risk and at high-risk of death.

Methods

The design, rationale, and primary results of the GISSI-HF study have been published elsewhere.[12-14] Briefly, the GISSI-HF was a randomized placebo-controlled nested trial designed to investigate the effects of n-3 polyunsaturated fatty acids and rosuvastatin on mortality and morbidity in patients with clinical evidence of stable chronic HF. The GISSI-HF was a pragmatic trial, with patients' enrollment performed between August 2002 and February 2005 by a network of 325 cardiology and 31 internal medicine representative Italian centers. The institutional review committee at each participating center approved the study, and all patients gave informed consent. Patients were enrolled irrespective of their age and left ventricular ejection fraction (LVEF), but their LVEF had to be measured within 3 months from enrolment. If it was higher than 40%, the patient had to have been admitted at least once to hospital for HF in the previous year to be included in the study. Patients were not excluded based on associated clinical conditions, and subjects with any comorbidity (including cancer) with a sufficiently long life expectancy were included. Detailed clinical data including patient characteristics, medical history, physical examination, 12-lead electrocardiogram, laboratories, medication use were collected at study enrollment. Causes of death recorded during follow-up were adjudicated blindly by an ad-hoc Committee on the basis of pre-agreed definitions and procedures, which included SCD (defined using the MERIT-HF criteria for sudden death[15] but excluding death from vascular cause, see Table II) and HF death (which death from worsening HF and/or pump failure). Patients allocated to n-3 polyunsaturated fatty acids showed a modest (9%) but significant reduction of all-cause mortality with respect to corresponding placebo,[14] while neutral results were observed for the rosuvastatin hypothesis.[13]

All variables needed to calculate the MAGGIC score[10] were available in the GISSI-HF database (see variables with ** in Table I). A total of 6975 ambulatory patients with chronic HF were enrolled in the GISSI-HF; 55 patients missed at least one of the 13 variables needed to estimate the MAGGIC score, and 61 were lost at 3-year follow-up, leaving a final sample for analysis of 6859 patients, with a mean follow-up of 3.5±1.3 years (range 1 to 6 years). Of note, the MAGGIC score was specifically designed to estimate 3-year probability of all-cause mortality, and the GISSI-HF sample was not part of the derivation cohort.[10]

Characteristics of patients at study enrollment are presented as means ±standard deviations, medians and interquartile ranges or frequencies and percentages, as appropriate.

The MAGGIC risk score was calculated according to the original model,[10] and the frequency of different modes of death patients was evaluated by quintiles of predicted MAGGIC risk of death, and compared using chi-squared test. ROC curves were obtained using logistic regression analysis, with the estimated MAGGIC probability of death tested separately against different outcomes (i.e. all-cause mortality, SCD, HF death). Area under the curves (AUC) and 95% confidence intervals were calculated using c-statistics, and compared using independent ROC curves analysis. Observed vs. predicted mortality rates were compared by increasing categories of risk, and the goodness of fit of the model was evaluated using the Hosmer-Lemeshow statistic. We finally investigated independent predictors of death and survival respectively in patients estimated at low-risk and at high-risk of death, using multivariate Cox regression analysis with backward selection of significant variables (criterion for variables to enter into the model was $P < .10$, criterion to stay in the model was $P < .05$). All statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, NC, USA).

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Results

Patients' characteristics

The overall characteristics of study population at enrollment are shown in Table I. Mean age was 67 years, 78% of patients were men and the majority of them

Table I. Overall characteristics of study population at enrollment

	N = 6859
CLINICAL CHARACTERISTICS	
**Age, years	67.2 ±10.7
**Body mass index, kg/m2	27.1 ±4.5
Heart rate, bpm	72.4 ±13.4
**Systolic blood pressure, mmHg	126.3 ±17.9
Diastolic blood pressure, mmHg	76.8 ±9.7
**Male sex, %	78.3
**NYHA class, %	
NYHA II	63.6
NYHA III	33.8
NYHA IV	2.6
Hepatomegaly, %	24.1
Pulmonary rales, %	25.1
Heart gallop (S3), %	24.9
CVP >6 cmH2O, %	11.9
Peripheral edema, %	25.2
MEDICAL HISTORY	
HF etiology, %	
Non-ischemic	50.2
Ischemic	49.8
Non-ischemic etiologies, %	
Dilated cardiomyopathy	29.0
Hypertensive cardiomyopathy	14.8
Alcoholic cardiomyopathy	0.8
Other or unknown	5.2
**Years of known HF, years	3.5 ±4.4
HF hospitalization within 1 year, %	48.4
Previous myocardial infarction, %	41.8
Previous coronary artery bypass grafting, %	18.3
Previous percutaneous coronary intervention, %	12.5
Previous internal cardioverter-defibrillator, %	7.1
Previous pacemaker, %	12.8
History of atrial fibrillation, %	19.0
Known peripheral arterial disease, %	8.8
History of cancer, %	3.7
Smoking status, %	
**Current	14.2
Previous (>1 year)	38.8
History of hypertension, %	54.6
**History of diabetes mellitus, %	28.3
**History of chronic obstructive pulmonary disease, %	22.0
ECG	
Heart rate, bpm	72.5 ±14.4
QRS duration, ms	117 ±36.6
Heart rhythm, %	
Sinus rhythm	72.8
Atrial fibrillation/flutter	16.4
Pacemaker	10.8
Bundle branch block	
Left	27.2
Right	6.4
Left ventricular hypertrophy, %	19.1
ECHOCARDIOGRAPHY	
**LVEF, %	33.1 ±8.5
LVEF groups, %	
<30	30.2
30-40	60.5
>40	9.3
LABS	
Hemoglobin, g/dl	13.7 ±1.7
Hemoglobin <12 mg/dL, %	14.0
White blood cell count, x103/mm3	7355.5 ±2116
Total cholesterol, mg/dL	190.7 ±42.9
HDL cholesterol, mg/ dL	47.2 ±13.3
LDL cholesterol, mg/ dL	115.8 ±36.3
Triglycerides, mg/dl	146.6 ±93.3
LDL cholesterol >100 mg/dL, %	58.6
LDL cholesterol <70 mg/dL, %	8.2
Serum uric acid, mg/ dL	6.7 ±2
Fibrinogen, mg/ dL	369.4 ±113.3
Fasting plasma glucose, mg/ dL	118.5 ±46.2
Glycosylated Hemoglobin, %	6.2 ±1.4
**Creatinine, mg/ dL	1.2 ±0.5
Estimated Glomerular Filtration rate, MDRD, ml/min/m2	68.1 ±23.3
Potassium, mEq/L	4.5 ±0.5
Sodium, mEq/L	140 ±3.8
Creatine Phosphokinase, U/L	88.5 ±61.6
MEDICATIONS	
Diuretics (excluding MRA), %	89.7
**ACEi/ARB, %	93.5
**β-Blockers, %	64.9
MRA, %	39.4
ACEi/ARB + β-Blockers, %	61.0
ACEi/ARB + β-Blockers + MRA, %	20.3
Amiodarone, %	19.5
Calcium channel blockers, %	10.1
Antiplatelet agents, %	56.3
Allopurinol, %	21.3
Statin treatment (open), %	22.8
Randomized to rosuvastatin, %	32.8
Statin treatment (open or randomized), %	56.6
Randomized to PUFA, %	50.2

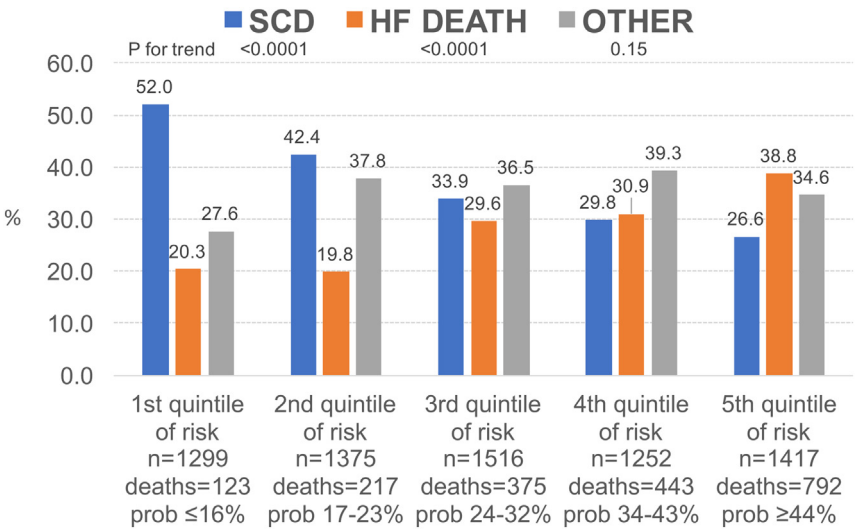
Variables contained in the MAGGIC model are indicated with **. NYHA = New York Heart Association functional class; LVEF = left ventricular ejection fraction; HF = heart failure; MDRD = modification of diet in renal disease formula; ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; MRA = mineralocorticoid receptor antagonists; PUFA = n-3 polyunsaturated fatty acids.

were in NYHA functional class II or III. About half of patients had ischemic HF. Mean heart rate was 72 bpm, and mean systolic and diastolic blood pressure was 126 and 77 mmHg, respectively. About 19% of patients had a history of atrial fibrillation, and 16% had atrial fibrillation at the enrollment ECG. About a third of patients had LVEF less than 30%, whereas the majority had LVEF between 30% and 40%, with only 9% having LVEF >40%. Background treatment included a blocker of the renin-angiotensin system in 94% of patients, a β-blocker in 65%, and a mineralocorticoid receptor antagonist in 40% of patients.

Modes of death and performance of the MAGGIC prediction model

The overall 3-year mortality was 28.4% (1950 deaths out of 6859 patients). The MAGGIC score predicted a mean mortality of 31.5%, giving an observed to expected ratio

Figure 1



Proportions of deaths at 3 year from sudden cardiac death, heart failure death, or death from other causes according to quintiles MAGGIC risk probability of death.

of 0.90, suggestive of overprediction. Average MAGGIC predicted mortality was 27.6% in alive patients, and 41.4% in those dead at follow-up.

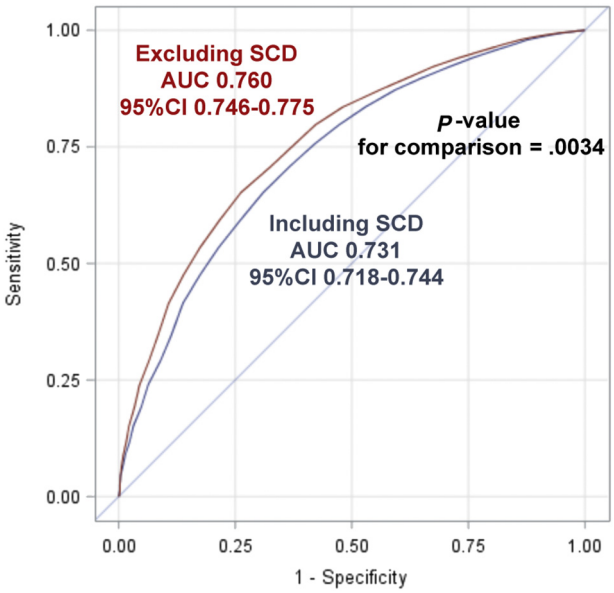
Causes of death were 1463 CV (21.3%; 75% of total mortality) and 487 non-CV (7.1%; 25% of total mortality). Modes of death were the following: 626 SCD (9.1%), 623 HF death (9.1%), 701 other deaths (10.2%); they accounted respectively for 32%, 32% and 36% of total mortality. Average MAGGIC estimated 3-year mortality was 37.4% in SCD, 45.7% in HF death and 41.0% in other deaths.

As a proportion of total deaths, the contribution from SCD progressively decreased with higher prognostic risk categories (i.e. quintiles of predicted MAGGIC risk), whereas the contribution from HF death progressively increased with higher risk categories (P <.0001for both), with other modes of death being relatively stable across risk groups (P = .15, see Figure 1). Mid-risk patients had a balanced combination of modes of death, with 34% of deaths due to SCD, 30% due to HF and 37% due to other causes (see Figure 1). These results were not significantly modified after removing 486 patients with an implanted ICD at study enrollment (see Supplemental Table I).

Accuracy of the MAGGIC model was good overall (ROC AUC 0.731, 95% CI 0.718-0.744). Nonetheless, the ROC AUC for 3-year mortality from SCD was 0.613 (95% CI, 0.591 to 0.636), whereas from HF death was 0.747 (95% CI, 0.728-0.766) and from other death was 0.688 (95% CI, 0.668-0.707).

Consistently, the overall accuracy of the MAGGIC model significantly improved after excluding those patients who died of SCD at follow-up (AUC 0.760, 95% CI 0.746-0.775, P for comparison = .0034, Figure 2). The

Figure 2

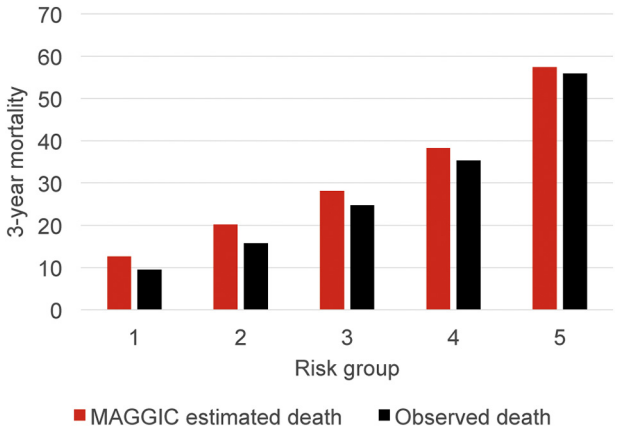


ROC curves before and after exclusion of SCD.

opposite was observed when excluding those patients who died of HF (AUC 0.705, 95% CI 0.689-0.721) or other causes (AUC 0.728, 95% CI 0.713-0.744), or a combination of these two (AUC 0.670, 95% CI 0.647-0.693).

The observed and predicted 3-year mortality are compared in Figure 3, which shows good calibration of the predicted and observed death probabilities across

Figure 3



Observed vs. model-predicted 3-year mortality by quintiles of MAGGIC risk probability of death.

quintiles of predicted risk; the Hosmer–Lemeshow test had $P > .50$, which confirms the goodness of fit of the model. Nonetheless, the gap between observed and predicted mortality decreased from 3.2% to 1.6% as the category of risk increased, indicating a more accurate calibration of the model in higher risk patients (Figure 3).

Analysis of prognostic outliers

The MAGGIC probability of death by death status at 3-year follow-up is shown in Figure 4.

Considering an observed 3-year mortality of about 28%, we defined the MAGGIC estimated risk of death to be indicative of "low-risk" when <14%, and of "high-risk" when >56%. These two boundaries correspond to half and double the observed death in the total population at 3-year follow-up, respectively. There were some unexpected dead (N = 61, i.e. patients observed dead at follow-up despite a low estimated risk of death) and some unexpected survivors (N = 210, i.e. patients observed alive at follow-up despite a high estimated risk of death) (Figure 4).

Unexpectedly dead patients (N = 61) were compared to those whose death was correctly predicted (i.e. patients dead with high risk of death, N = 375). As shown in Table II, the prevalence of CV deaths was similar in the two groups, but more than half of unexpected deaths occurred because of SCD, which was significantly less frequent in those expected dead at follow-up (52.5% in unexpected dead vs. 23.5% in expected deaths, $P < .0001$). On the contrary, CV death from worsening HF was significantly more frequent in the latter group (19.7% in unexpected dead vs. 46.1% in expected dead, $P < .0001$).

As predictable, all the components of the MAGGIC score were significantly different between the two groups, i.e. those unexpectedly dead as compared to those expected dead were younger at enrollment, with higher systolic blood pressure and BMI, a lower prevalence of diabetes mellitus and chronic obstructive pulmonary disease (COPD), a more preserved LVEF and renal function, a lower NYHA functional class, a longer history of HF, and a greater use of ACEi/ARB and β-blockers (Supplemental Table II). In addition, patients unexpectedly dead had less congestion at enrollment, had a slower heart rate and narrower QRS, a lower prevalence of atrial fibrillation and implanted pacemaker, a more prevalent non-ischemic HF etiology, less anemia and a worse lipid profile and a lesser use of diuretics, mineralocorticoid receptor antagonists, amiodarone and allopurinol (Supplemental Table II). On the other hand, unexpected survivors (N = 210) were compared to those whose survival was correctly predicted (i.e. alive with low risk of death, N = 743). The comparison between these two groups showed results that were specular to those found comparing expected vs. unexpected dead (Supplemental Table III). In addition, unexpected survivors had more ICD already been implanted at study enrollment, a higher prevalence of left bundle branch block and a greater use of statins (Supplemental Table III).

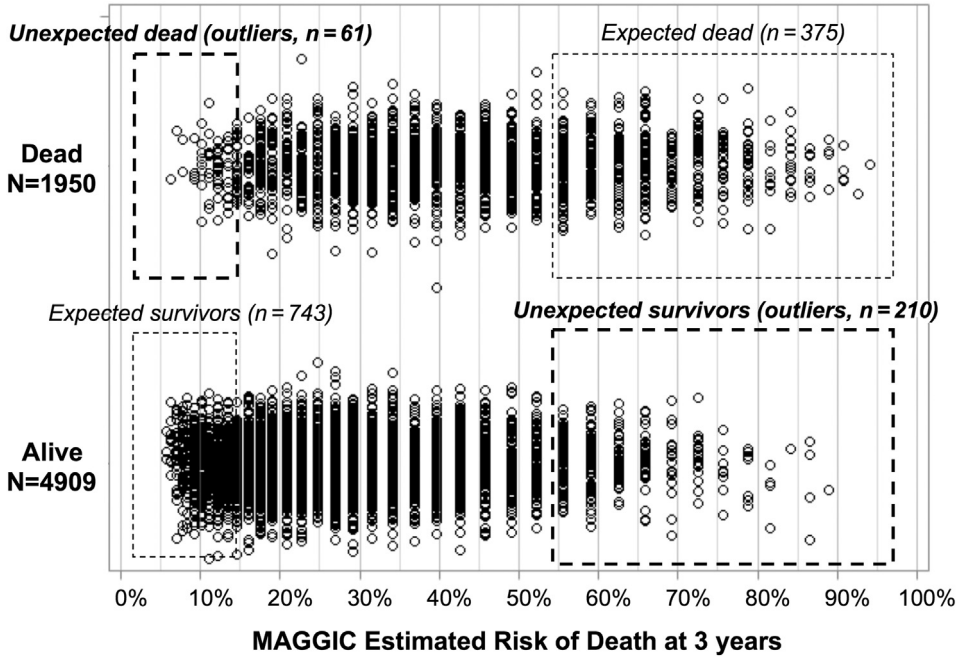
We finally separately investigated independent predictors of death and survival respectively in the groups estimated at low-risk and at high-risk of 3-year mortality. There were 743 alive patients and 61 dead patients in the low-risk population (Figure 4), and among them, independent predictors of death were older age, longer history of HF, COPD and higher serum uric acid (Table III.A). On the other hand, there were 210 alive patients and 375 dead patients in the high-risk population (Figure 4); in this sample, the only independent predictor of survival was higher systolic blood pressure (Table III.B).

Discussion

The present analysis indicates that the accuracy of the MAGGIC risk score in predicting all-cause mortality significantly increases when excluding SCD from the mortality outcome. The calibration of the MAGGIC score increases in the highest categories of risk, possibly due to the decreasing incidence of SCD in these groups. Thus, as the older SHFM,[9] the MAGGIC risk score demonstrates its scarce ability to capture SCD, particularly in HF subjects estimated to be at low risk of death when considering the usual 13 cardiac and extra-cardiac components of the score.

The SHFM had been already shown to be more accurate in the stratification of the risk of nonsudden death compared with SCD,[9,16] and this result was reproduced here using the most recent MAGGIC score and a more contemporary population of ischemic and nonischemic patients with HFrEF from the GISSI-HF trial. The MAGGIC score appeared to be even less accurate than the SHFM in predicting SCD, with an AUC of 0.61 vs. 0.66-0.68 for SHFM in previous works.[9,17] Due to the widespread

Figure 4



Three-year MAGGIC estimated risk of death and actual death.

Table II. Clinical outcome in expected vs. unexpected deaths

	Expected dead (N = 375)	Unexpected dead (outliers, N = 61)	*P*
Outcomes			
Cause of death			.73
CV death	78.4	80.3	
Non-CV death	21.6	19.7	
Mode of death			.0007
Worsening heart failure	46.1	19.7	
Presumed arrhythmic	20.3	50.8	
Acute coronary syndrome	2.4	1.6	
Stroke	4.8	3.4	
Other CV reasons	4.8	4.9	
Neoplasia	6.4	6.5	
Other non-CV reasons	12.5	9.8	
Not known	2.7	3.3	
Adjudicated SCD	23.5	52.5	<.0001
Type of SCD			<.0001
Witnessed instantaneous death in the absence of progressive circulatory failure lasting for 60 min or more	8.8	19.7	
Unwitnessed death in the absence of pre-existence progressive circulatory failure or other causes of death	11.5	26.3	
Death within 28 days after resuscitation from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death, death during attempted resuscitation	0.3	1.6	
Death within 60 min from the onset of new symptoms unless a cause other than cardiac was obvious	2.9	4.9	

implementation of evidence-based medications, the overall risk of sudden death (which includes SCD) in HFrEF has been declining over time,[3] with an annual rate as low as 3.3% and a 3-year cumulative incidence of 8.8% in most recent clinical HFrEF trials, including the GISSI-HF one.[4] Thus, SCD is becoming a rather rare event over

Table III. Independent predictors of death in patients estimated at low-risk and high-risk by the MAGGIC score

	HR	95% CI LL	95% CI UL	Chi-square	*P*
A. Low-risk group – predictors of DEATH					
Age, 5 years	1.395	1.161	1.676	12.6	.0004
Years of HF, 5 years	1.342	1.023	1.759	4.5	.0336
History of COPD	2.919	1.154	7.386	5.1	.0237
Serum uric acid, mg/dL	1.370	1.006	1.322	4.9	.0409
B. High-risk group – predictors of SURVIVAL					
Systolic blood pressure, 5 mmHg	1.047	1.009	1.086	5.9	.0145

Models included the following variables: age, gender, BMI, heart rate, systolic blood pressure, hemoglobin, white blood cell count, total cholesterol, uricemia, glycemia, potassium, sodium, creatinine, years of HF, NYHA class, heart gallop, atrial fibrillation at ECG, left bundle branch block at ECG, ischemic etiology, previous hospitalization, history of hypertension, history of myocardial infarction, previous coronary revascularization, implanted ICD, implanted pacemaker, history of peripheral arterial disease, history of atrial fibrillation, history of COPD, current smoking, previous cancer, LVEF, diuretics, ACEi/ARB, β-blockers, MRA, amiodarone, antiplatelet drugs, statin therapy (open or randomized).

time, a fact that makes its prediction even more difficult. Specific models have been developed for the prediction of SCD in the general population[18,19] and in HF populations,[20] but their ability to discriminate between the risk of sudden and nonsudden death remains poor. The Seattle Proportional Risk Model has been recently proposed to this goal[21] and as an addendum to the older SHFM, providing an effective assessment of how overall survival with the SHFM is modified by ICD implantation.[22] However its validation has been limited so far, and primarily based on the magnitude of the ICD-associated improvement in survival relative to control rather than on actual sudden and nonsudden death events.[22] Thus, current recommendations for implanting an ICD for primary prevention of SCD in HFrEF patients still rely on a NYHA II-III functional class and a LVEF≤35%.[23,24] The sensitivity of both NYHA and LVEF for prediction SCD is poor,[25] and our analysis further confirms that a large number of SCD events occurred in patients with a lower NYHA functional class and a more preserved LVEF. More sensitive predictors of SCD, including myocardial fibrosis by magnetic resonance imaging, have been proposed,[25] but their availability is limited, it is costly and to date it is still unclear whether their addition to NYHA and LVEF will sufficiently improve SCD risk stratification.[26]

Among patients with HF, a subset has a high risk of death due to progression of HF rather than SCD. Ideally prognostic risk scores, by incorporating multiple variables, should provide a more comprehensive assessment of the whole patient population and therefore better capture this risk. Accordingly, our analysis showed a significant positive relationship between increasing MAGGIC score and death due to worsening HF and pump failure. Beyond age and gender, the MAGGIC includes 6 cardiovascular variables (LVEF, systolic blood pressure, NYHA class, diagnosis of HF within 18 months, no β-blocker use, no ACEi/ARBs) and 5 extra-cardiac ones (BMI, creatinine, current smoking, diabetes, COPD). Noncardiac comorbidity burden is nowadays recognized to be higher in HFpEF than in HFrEF population,[27] from which the majority of available prognostic scores where designed.[8] In addition, a recent analysis investigated the contribution of cardiac and extra-cardiac components of the MAGGIC risk score to mortality in HFpEF vs. HFrEF patients, and found that extra-cardiac burden accounted for a greater proportion of risk for death than cardiac burden in HFpEF patients, whereas in HFrEF patients the highest risk of death and CV death was attributable to cardiac burden.[28] Thus, there is a need for new effective prognostic tools that can cover the full spectrum of the HF disease, properly balance the contribution of cardiac and extra-cardiac components, and specifically target the competitive arrhythmic vs. end-stage pump failure risk of death.

A recent review manuscript analyzed more than 40 models for the prediction of risk of death in HF, and identified the following common variables as consistent and strong predictors of risk across studies: age, renal function, blood pressure, sodium level, LVEF, sex, NYHA functional class, diabetes, weight/body mass index, exercise capacity and natriuretic peptide.[29] The MAGGIC score includes all of these variables except exercise capacity and natriuretic peptide, but has the advantage of a very large derivation cohort of about 40,000 HF patients from wide geographic region and type of studies (both observational and randomized).[10] COPD is included in the MAGGIC model, but still emerged as an independent predictor of death in those estimated at low risk (i.e. 3-year mortality <14%), further demonstrating the contribution of this chronic condition, both correctly and incorrectly labeled, to worsening long-term prognosis of HF patients.[30] In the same low-risk group, hyperuricemia also emerged as an independent marker of increased mortality. This parameter is not included in the MAGGIC, but it is instead a component of the GISSI-HF[31] and the SHFM[32] prognostic scores. Several clinical studies,[33] including the recent PARADIGM-HF,[34] have identified elevation of serum uric acid as an independent marker of worse HF prognosis, but xanthine oxidase inhibition with allopurinol failed to improve clinical outcome in patients with HFrEF and serum uric acid levels ≥9.5 mg/dL.[35] The role of hyperuricemia in HF patients with more preserved LVEF (a peculiar characteristics of our low-risk group) has been less extensively

explored[36] and deserves more attention. On the contrary, higher systolic blood pressure was associated with increased survival in the high-risk group (i.e. with estimated 3-year mortality >56%). Whereas hypertension is deleterious at the earlier stages of HFrEF, a low systolic blood pressure is often associated with poor outcomes in more advanced HFrEF.[37] This association has been historically attributed to progressive cardiac pump failure at advanced HFrEF stages, but it was recently shown in hospitalized HFpEF patients,[38] which makes reverse causation in HFrEF less likely, and points to low systolic blood pressure as a convenient and crucial prognostic marker of adverse prognosis for the whole HF population.

Finally, we isolated "prognostic outliers" (i.e. patients found unexpectedly dead or alive at follow-up) with the goal of phenotyping a subgroup of patients that in daily clinical practice would deserve a greater attention by cardiologists, because of the inability of current prognostic tools to correctly predict their risk of death. A recent analysis used a similar approach to analyze individual prediction in an administrative dataset of 9282 HF patients with a 1-year mortality of 17.9%.[11] However, the dataset lacked several relevant MAGGIC score variables (LVEF, body mass index, systolic blood pressure, serum creatinine and smoking status), and a 1-year probability of death as high as 50% was used for differentiating patients at low- and high-predicted risk of death. Instead of using a unique arbitrary 50% threshold, we elected to base our stratification on our observed 28% 3-year mortality, and set the two boundaries of 14% and 56% to differentiate low- and high-predicted risk, respectively, and identify those that we named "prognostic outliers". This approach prevented us from performing sensitivity and specificity analysis, but allowed to separate what we believe are "true prognostic outliers", i.e. 61 dead in 804 low-risk patients (unexpected deaths, 7.6%) and 210 survivors in 585 high-risk patients (unexpected survivals, 35.9%), scaling down previous estimations.[11] Nonetheless, SCD emerged as a frequent and unexpected cause of death in the low-risk group, occurring in 52.5% of these patients (vs. only in 23.5% of the high-risk ones). This uncertainty inherent in survival estimates should be openly acknowledged when dealing with patients and other healthcare providers, and should drive future research initiatives in this area.

There are strengths and limitations in this study that warrant a brief discussion. Among the strengths, we tested the externally validated MAGGIC model in the GISSI-HF population, an independent sample that did not contribute to the MAGGIC meta-analysis.[10] The GISSI-HF dataset proved valuable to our analysis because it constituted a large cohort of HFrEF patients i) enrolled in a pragmatic trial with wide inclusion criteria, thus very similar to a population study; ii) randomized to medications that had marginal effect (n-3 PUFA) or no effect (rosuvastatin) on all-cause mortality that we herein investigated; iii) treated according to current clinical practice, iv) followed for approximately 3 years, the follow-up period for which the MAGGIC was specifically designed. A previous similar analysis tested the older SHFM in a sample derived from six mixed studies with different designs and completed before the year 2000. In the final sample, prevalence of β-blockers use was only 31%, and follow-up was limited at 1 year with a mortality as high as 19.1%.[9] In addition, the Authors of this work examined sudden death as a whole, whereas we were able to specifically investigate SCD, which was adjudicated blindly by an ad-hoc Committee on the basis of pre-agreed definitions and procedures.[12] Nonetheless, criteria for SCD definition varies widely across HF studies, and sufficient details to distinguish SCD from the broader syndrome of sudden death are frequently lacking.[1] Thus, other events such as acute respiratory failure or massive pulmonary embolism rather than cardiac arrhythmias might represent a precipitating cause of sudden death in HF patients,[39] particularly those with more preserved LVEF and greater comorbidity burden; this potential source of error, which is intrinsic to all contemporary HF trials, needs to be taken into account. In addition, our analysis neither accounted for aborted SCD due to successful resuscitation after cardiac arrest nor for life-saving ICD discharges. We lack information on whether ICD were implanted for primary or secondary prevention of SCD. However, when performing sensitivity analysis excluding 486 patients with an implanted ICD at baseline (7.1%), results remained unchanged. Future studies should however prospectively include these aborted events among the SCD-related endpoints[40] to better explore the relationship between risk of HF death and incident SCD, which might likely be U-shaped. Furthermore, only 64.9% of patients in the GISSI-HF were receiving a β-blocker at study enrollment, whereas this percentage approaches 93% in most contemporary HFrEF registries[41] and trials[42]; thus, our results should be interpreted in the light of this further limitation. Finally, no prognostic biomarkers such as troponin or natriuretic peptides were systematically detected and available for analysis.

In conclusion, available prognostic scores for HF patients have been primarily designed to predict total mortality, and do not properly capture the risk of SCD. Our analysis demonstrated that the most updated MAGGIC score suffers the same lack of accuracy, particularly in HFrEF patients, who are predicted to be at low-risk of death but experience a greater number of unexpected SCD. These patients have outliers' characteristics that do not allow performing a correct risk stratification using standard approaches, and may require a more individualized assessment, which would likely include appropriate additional imaging and biomarker evaluations yet to be determined. The power of any

available prognostic model should be updated whenever the HF scenario changes and prognosis improves. The increasing burden of HFpEF and the steadily decline in sudden death experienced by HFrEF patients in the last two decades demand for newer and better prognostic tools specifically designed for clinicians to make the best prediction in this evolving horizon.

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All members reviewed the paper and unanimously agreed to submit it to the journal.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.11.009.

References

1. Vaduganathan M, Patel RB, Michel A, et al. Mode of death in heart failure with preserved ejection fraction. J Am Coll Cardiol 2017;69:556-69.
2. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-40.
3. Cubbon RM, Gale CP, Kearney LC, et al. Changing characteristics and mode of death associated with chronic heart failure caused by left ventricular systolic dysfunction: a study across therapeutic eras. Circ Heart Fail 2011;4:396-403.
4. Shen L, Jhund PS, Petrie MC, et al. Declining risk of sudden death in heart failure. N Engl J Med 2017;377:41-51.
5. Vaduganathan M, Michel A, Hall K, et al. Spectrum of epidemiological and clinical findings in patients with heart failure with preserved ejection fraction stratified by study design: a systematic review. Eur J Heart Fail 2016;18:54-65.
6. Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. Circulation 2012;125:1043-52.
7. Alba AC, Agoritsas T, Jankowski M, et al. Risk prediction models for mortality in ambulatory patients with heart failure: a systematic review. Circ Heart Fail 2013;6:881-9.
8. Canepa M, Fonseca C, Chioncel O, et al. Performance of prognostic risk scores in chronic heart failure patients enrolled in the European Society of Cardiology Heart Failure Long-Term Registry. JACC Heart Fail 2018;6:452-62.
9. Mozaffarian D, Anker SD, Anand I, et al. Prediction of mode of death in heart failure: the Seattle Heart Failure Model. Circulation 2007;116:392-8.
10. Pocock SJ, Ariti CA, McMurray JJ, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J 2013;34:1404-13.
11. Allen LA, Matlock DD, Shetterly SM, et al. Use of risk models to predict death in the next year among individual ambulatory patients with heart failure. JAMA Cardiol 2017;2:435-41.
12. Tavazzi L, Tognoni G, Franzosi MG, et al. Rationale and design of the GISSI heart failure trial: a large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. Eur J Heart Fail 2004;6:635-41.
13. Gissi HFI, Tavazzi L, Maggioni AP, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1231-9.
14. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1223-30.
15. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) Lancet 1999;353:2001-7.
16. Levy WC, Hellkamp AS, Mark DB, et al. Improving the use of primary prevention implantable cardioverter-defibrillators therapy with validated patient-centric risk estimates. JACC Clin Electrophysiol 2018;4:1089-102.
17. Levy WC, Lee KL, Hellkamp AS, et al. Maximizing survival benefit with primary prevention implantable cardioverter-defibrillator therapy in a heart failure population. Circulation 2009;120:835-42.
18. Aro AL, Reinier K, Rusinaru C, et al. Electrical risk score beyond the left ventricular ejection fraction: prediction of sudden cardiac death in the Oregon Sudden Unexpected Death Study and the Atherosclerosis Risk in Communities Study. Eur Heart J 2017;38:3017-25.
19. Deo R, Norby FL, Katz R, et al. Development and validation of a sudden cardiac death prediction model for the general population. Circulation 2016;134:806-16.
20. Shadman R, Poole JE, Dardas TF, et al. A novel method to predict the proportional risk of sudden cardiac death in heart failure: derivation of the Seattle Proportional Risk Model. Heart Rhythm 2015;12:2069-77.
21. Levy WC, Li Y, Reed SD, et al. Does the implantable cardioverter-defibrillator benefit vary with the estimated proportional risk of sudden death in heart failure patients? JACC Clin Electrophysiol 2017;3:291-8.
22. Bilchick KC, Wang Y, Cheng A, et al. Seattle heart failure and proportional risk models predict benefit from implantable cardioverter-defibrillators. J Am Coll Cardiol 2017;69:2606-18.
23. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.
24. Yancy CW, Jessup M, Bozkurt B, et al. ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;2017.
25. Halliday BP, Cleland JGF, Goldberger JJ, et al. Personalizing risk stratification for sudden death in dilated cardiomyopathy: the past, present, and future. Circulation 2017;136:215-31.
26. Arbustini E, Disertori M, Narula J. Primary prevention of sudden arrhythmic death in dilated cardiomyopathy: current guidelines and risk stratification. JACC Heart Fail 2017;5:39-43.

27. Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol 2012;59:998-1005.
28. Wolsk E, Claggett B, Kober L, et al. Contribution of cardiac and extracardiac disease burden to risk of cardiovascular outcomes varies by ejection fraction in heart failure. Eur J Heart Fail 2018;20:504-10.
29. Rahimi K, Bennett D, Conrad N, et al. Risk prediction in patients with heart failure: a systematic review and analysis. JACC Heart Fail 2014;2:440-6.
30. Canepa M, Temporelli PL, Rossi A, et al. Prevalence and prognostic impact of chronic obstructive pulmonary disease in patients with chronic heart failure: data from the GISSI-HF Trial. Cardiology 2017;136:128-37.
31. Barlera S, Tavazzi L, Franzosi MG, et al. Predictors of mortality in 6975 patients with chronic heart failure in the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure trial: proposal for a nomogram. Circ Heart Fail 2013;6:31-9.
32. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation 2006;113:1424-33.
33. Anker SD, Doehner W, Rauchhaus M, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003;107:1991-7.
34. Mogensen UM, Kober L, Jhund PS, et al. Sacubitril/valsartan reduces serum uric acid concentration, an independent predictor of adverse outcomes in PARADIGM-HF. Eur J Heart Fail 2018;20:514-22.
35. Givertz MM, Anstrom KJ, Redfield MM, et al. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients: the Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) Study. Circulation 2015;131:1763-71.
36. Palazzuoli A, Ruocco G, De Vivo O, et al. Prevalence of hyperuricemia in patients with acute heart failure with either reduced or preserved ejection fraction. Am J Cardiol 2017;120:1146-50.
37. Kalantar-Zadeh K, Block G, Horwich T, et al. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. J Am Coll Cardiol 2004;43:1439-44.
38. Tsimploulis A, Lam PH, Arundel C, et al. Systolic blood pressure and outcomes in patients with heart failure with preserved ejection fraction. JAMA Cardiol 2018:288-97.
39. McGarvey LP, John M, Anderson JA, et al. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. Thorax 2007;62:411-5.
40. Vaduganathan M, Claggett BL, Chatterjee NA, et al. Sudden death in heart failure with preserved ejection fraction: a competing risks analysis from the TOPCAT Trial. JACC Heart Fail 2018;6:653-61.
41. Maggioni AP, Anker SD, Dahlstrom U, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2013;15:1173-84.
42. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.