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A multiparametric heart failure score at baseline is associated with long-term outcome in patients with remotely monitored implantable cardioverter-defibrillators: A pooled analysis of 9 clinical trials

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ABSTRACT

BACKGROUND To predict worsening heart failure hospitalizations (WHFHs), the HeartInsight multiparametric algorithm calculates a heart failure (HF) Score based on temporal trends of physiologic parameters obtained through automatic daily remote monitoring of implantable cardioverter-defibrillators (ICDs).

OBJECTIVE We studied the association of the baseline HF Score, determined at algorithm activation, with long-term patient outcomes.

METHODS Data from 9 clinical trials were pooled, including 1841 ICD patients with a preimplantation ejection fraction ≤35%, New York Heart Association class II/III, and no long-standing atrial fibrillation. The primary end point was a composite of death or WHFH.

RESULTS After a median follow-up of 631 days (interquartile range, 385–865 days), there were 243 WHFHs in 173 patients (9.4%) and 122 deaths (6.6%), 52 of which (42.6%) were cardiovascular. The primary end point occurred in 265 patients (14.4%). A multivariable time-to-first-event analysis showed that a high baseline HF Score (>23, as determined by a time-dependent receiver operating characteristics curve analysis) was significantly associated with the occurrence of the primary end point (adjusted hazard ratio [HR], 2.05; 95% confidence interval [CI], 1.54–2.71; $P < .0001$), all-cause death (HR, 2.37; CI, 1.56–3.58; $P < .0001$), cardiovascular death (HR, 2.19; CI, 1.14–4.22; $P = .019$), and WHFH (HR, 1.91; CI, 1.35–2.71; $P = .0003$). In a hierarchical event analysis of all-cause death as the outcome with highest priority and WHFHs as repeated event outcomes, the win ratio was 2.47 (CI, 1.89–3.24; $P < .0001$).

CONCLUSION Based on a retrospective analysis of clinical trial data with adjudicated events, baseline HF Score derived from device-monitored variables was able to stratify patients at higher long-term risk of death or WHFH.

KEYWORDS Death; Heart failure score; Implantable defibrillator; Risk stratification in heart failure patients; Remote monitoring; Worsening heart failure hospitalization

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Introduction

To predict worsening heart failure (WHF) in patients with implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy defibrillators (CRT-Ds), the HeartInsight feature (Biotronik SE & Co KG, Berlin, Germany) calculates a heart failure (HF) Score by evaluating temporal trends of physiologic parameters obtained by automatic daily remote monitoring of implanted devices.[1] In the Selection of

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Potential Predictors of Worsening Heart Failure (SELENE HF) study, the HeartInsight algorithm (optionally combined with a clinical risk stratifier, the Seattle Heart Failure Model [SHFM])[2] was shown to predict impending WHF hospitalizations (WHFHs) with good sensitivity and low false-alert rate.[1] Botto and coworkers[3] thereafter analyzed temporal trends in HF Scores and found that the mean HF Score was already ≈35% higher 12 weeks before WHFH than the mean score in patients without WHFHs, further to increase by 22% toward the event.

Therefore, as a next step in the research of HeartInsight, we investigated whether the initial values of the HF Score at the time of algorithm activation are associated with the patient's outcomes in the long term. Specifically, we studied the association between the baseline HF Score (determined as the average HF Score during 1 week after HeartInsight activation) and the composite of all-cause death or WHFH during follow-up. The results will provide insights into the clinical utility of the baseline HF Score as a risk stratifier, identifying high-risk patients who may require closer monitoring, continuous therapy optimization, and prompt reactions to alerts or findings.

Methods

Selection of studies and patients for pooled analysis

For this retrospective analysis, we selected all completed or ongoing clinical trials in which full access to the patient-level remote monitoring data set was available and in which patients fulfilling the conditions for HeartInsight activation could be recruited on the basis of the study inclusion and exclusion criteria. According to the instructions for use of the HeartInsight feature, patients contributed to the analysis if they had a CRT-D or an ICD capable of atrial sensing (a dual-chamber ICD or a DX ICD with a floating atrial dipole on the ICD lead[4]), left ventricular ejection fraction (LVEF) ≤35%, New York Heart Association (NYHA) class II or III HF at device implantation, no long-standing persistent or permanent atrial fibrillation (AF), all required diagnostic features active (eg, thoracic impedance measurements), and remote monitoring transmissions available for the HF Score computation.

Abbreviations

AF: atrial fibrillation

CRT-D: cardiac resynchronization therapy defibrillator

HM: Home Monitoring

HR: heart rate

ICD: implantable cardioverter-defibrillator

LVEF: left ventricular ejection fraction

SHFM: Seattle Heart Failure Model

WHFH: worsening heart failure hospitalization

Predictive algorithm and baseline HF Score

HeartInsight is integrated into the Home Monitoring (HM) platform. In normal operating conditions, the algorithm calculates the HF Score daily by evaluating temporal trends of 7 longitudinal HM parameters collected during the preceding 90 days: 24-hour heart rate (HR), nocturnal HR, HR variability, atrial tachyarrhythmia, ventricular extrasystoles, physical activity, and thoracic impedance.[1,3] The system alerts clinical staff to an increased risk of WHFH when the HF Score exceeds a programmable threshold with a default value of 45.[3]

For this analysis, activation of HeartInsight was simulated on day 90 of remote monitoring, when the algorithm is first expected to compute the HF Score based on complete information by the algorithm design. The baseline HF Score was calculated as an average of daily HF Score values obtained during 1 week after HeartInsight activation. Depending on the protocol requirements of the included trials, remote monitoring was activated generally, but not systematically, at device implantation. The optional SHFM score was not available in all included studies, and we omitted it consistently in all patients to assess the predictive value of solely device-monitored variables.

Study end points

The primary end point was the composite of WHFH or death from any cause after the simulated HeartInsight activation, with a blanking period of 7 days for baseline HF Score calculation. Secondary end points were WHFH, all-cause death, and cardiovascular death. All WHFHs in the pooled trials were adjudicated according to the same criteria, defining this event as a nonelective hospital admission with overnight stay, triggered by symptoms and signs or objective evidence of WHF and requiring administration of intravenous therapy for HF (diuretics, vasodilators, or inotropic agents).

Study objectives and methods

The primary objective of the analysis was to assess the association of the baseline HF Score with the primary end point both in a time-to-first-event analysis and in a prioritized analysis, hierarchically including deaths as the outcome with highest importance and any recurrent WHFH as a repeated event outcome. We further assessed the association of the baseline HF Score separately with the secondary end points in a time-to-first-event analysis. All calculations were post hoc, based on the prospectively collected HM and end point data before the availability of the HeartInsight feature. For ongoing trials, database lockout was on November 29, 2022.

Patients were excluded from the analyses if they discontinued the study or the primary end point occurred before the supposed calculation of baseline HF Score (97 days after the first HM message).

Statistical methods

Time-to-first-event analyses were performed with univariable and multivariable Cox proportional hazards models stratified by clinical trial to estimate survival to the primary end point and secondary end points, depending on the baseline HF Score. Unadjusted and adjusted hazard ratios and 95% confidence intervals (CIs) were reported. Adjusting covariates were patient age, sex, body mass index, AF history, NYHA class, device type (CRT-D/ICD), HF cause, renal insufficiency, chronic pulmonary disease, diuretic use, and digitalis use. These covariates were selected by either their known

association with the combined primary end point of WHFH and mortality or their significant imbalance between the subgroups with and without primary end point events. Then, the most relevant subset of covariates was determined through a stepwise selection procedure using the Akaike information criterion. The baseline HF Score was treated both as a continuous variable and as a binary variable after splitting the study population by a cutoff value determined with a time-dependent receiver operating characteristic (ROC) curve estimated with the nearest neighbor method. The cutoff value was determined by identifying the closest point to perfect classification at 1 year, 2 years, 3 years, and 4 years. Kaplan-Meier plots for primary and secondary end points were thereafter compared for a baseline HF Score above vs below the cutoff value by using the log-rank test. The primary end point of death or recurrent WHFHs was finally analyzed in the 2 subgroups (baseline HF Score above vs below the cutoff value) with the win ratio analysis to account for the different order of importance of death (highest priority) and multiple WHFHs recurring in same individuals: death was the time-to-event outcome, WHFHs were repeated event outcomes.[5] The win ratio of "low" (equal to or below cutoff) vs "high" (above cutoff) baseline HF Score was reported along with the 95% CI.

The HeartInsight algorithm was originally developed and validated in the SELENE HF trial,[1] which is included in this study's pool. As a sensitivity analysis, we therefore repeated time-to-first-event analyses by excluding data from the SELENE HF trial.

Other continuous data are compared by the Mann-Whitney *U* test and reported as median with interquartile range (IQR) after the Shapiro-Wilks test indicated nonnormal distributions. Categorical data are reported as absolute and relative frequencies and compared by the Pearson χ^2 or Fisher exact test as appropriate.

In all cases, a *P* value < .05 was considered statistically significant. The analyses were performed with the STATA/MP 18.0 (StataCorp LLC, College Station, TX) and R statistical software (version 4.3; R Core Team 2023, https://www.R-project.org/; main R packages: StepReg, survivalROC, survival, and WinRatio).

Results

Eight trials conducted between 2008 and 2020 (CASTLE-AF,[6] DetectICI, EchoCRT,[7] ECOST-CRT,[8] effecT, HomeCARE II,[9] J-HomeCARE II,[9] SELENE HF[1]) and 1 ongoing trial (BIO-|Stream.HF[10]) met the study inclusion criteria. The explanation of the acronyms, objectives, size, and duration of these trials can be found in Supplemental Table S1.

The pooled trials included a total of 5987 patients. After a stepwise patient selection according to the clinical, technical, and analysis-specific exclusion criteria, the final analysis set included 1841 patients (Figure 1). Because of protocol requirements and different time periods and geographic locations of the studies, double recruitment was not possible. Supplemental Table S2 shows distribution of patients and end points per clinical trial.

Follow-up duration, events, and demographics

During a median follow-up period of 631 days (IQR, 385–865 days), there were 243 WHFHs in 173 patients (9.4%) and 122 deaths from any cause (6.6%), 52 of which (42.6%) were cardiovascular, 59 (48.4%) noncardiovascular, and 11 (9.0%) from unknown causes. Two deaths from COVID-19 in the BIO-|Stream.HF study (the only study ongoing during the COVID-19 pandemic) were classified as noncardiovascular. The primary end point occurred in 265 patients (14.4%), with a rate of 7.7 per 100 patient-years, ranging from 5.4 (BIO-|Stream.HF) to 13.4 (CASTLE-AF) per 100 patient-years.

The baseline characteristics of the patients are summarized in Table 1. Compared with the group without events, the 265 patients who experienced the primary end point event were slightly older (median 69 vs 67 years; $P = .003$) and had a greater prevalence of NYHA class III (60.8% vs 52.1%; $P = .009$), ischemic cause (57.0% vs 47.2%; $P = .003$), history of AF (33.9% vs 19.7%; $P < .001$), renal insufficiency (30.5% vs 17.7%; $P < .001$), and chronic pulmonary disease (20.6% vs 15.1%; $P = .026$). Patients experiencing primary end point events were also more likely to be receiving diuretics, antiplatelets, anticoagulants, antiarrhythmic drugs, and digitalis.

The median HM transmission success rate during follow-up was 93.2% (IQR, 85.5%–97.7%). The median time from device implantation to remote monitoring activation was 4 days (IQR, 1–18 days).

Baseline HF Score and its association with end points

The median baseline HF Score in the period 90–97 days after remote monitoring activation was 22.2 (IQR, 15.7–30.0). When stratified by the occurrence of the primary end point (yes/no), the distribution of baseline HF Scores showed a clear distinction between the groups (Figure 2), with a median of 27.1 (IQR, 20.6–37.7) in the group with primary end point events and 21.5 (IQR, 15.3–29.0) in the group without primary end point events ($P < .0001$).

In the time-to-first-event analysis, the baseline HF Score was significantly associated with the primary end point when treated as a continuous variable in the Cox regression analysis, with a hazard ratio of 1.03 (95% CI, 1.02–1.04; $P < .0001$) for unitary score increase (Table 2). Renal insufficiency, history of AF, ischemic cause, and diuretic use were significant covariates. The time-dependent ROC curve analysis for years 1–4 (Supplemental Figure S1) consistently resulted in a cutoff for the baseline HF Score of 23, with true-positive and false-positive rates ranging from 62% to 65% and from 38% to 42%, respectively (C statistics, 0.63–0.65). When treated as a binary variable (high score, >23; low score, ≤23) in the multivariable Cox regression analysis (Table 3), the baseline HF Score was significantly associated with the primary end point, all-cause death, cardiovascular death, and WHFH. Adjusted hazard ratio between high and low scores for the primary end point was 2.05 (95% CI, 1.54–2.71; $P < .0001$); for secondary end points, it ranged from 1.91 (WHFH) to 2.37 (all-cause death).

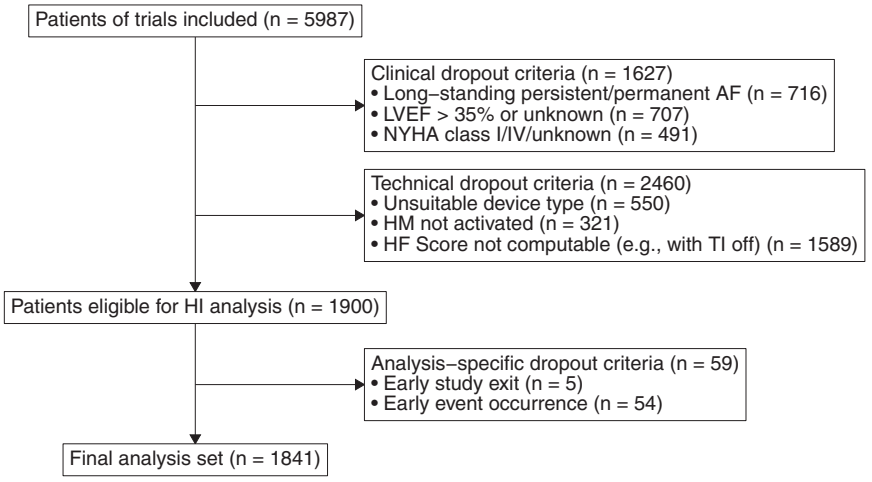

Figure 1
Patient attrition chart shown as a Consolidated Standards of Reporting Trials flow diagram. AF = atrial fibrillation; HF = heart failure; HI = HeartInsight; HM = Home Monitoring; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TI = thoracic impedance.

Table 1 Baseline characteristics of patients

Parameter[a]	All patients (N = 1841)	Patient group: Primary end point (n = 265)	Patient group: No primary end point (n = 1576)	*P* value
Age, years	67 (60–74)	69 (63–75)	67 (59–74)	.003
Male sex	1413 (76.8)	207 (78.1)	1206 (76.5)	.571
Body mass index, kg/m^2	26.8 (24.0–30.3)	27.0 (24.1–30.4)	26.8 (24.0–30.3)	.493
NYHA class				.009
II	859 (46.7)	104 (39.2)	755 (47.9)	
III	982 (53.3)	161 (60.8)	821 (52.1)	
LVEF, %	29 (25.0–32.0)	28 (24.0–31.0)	29 (25.0–32.0)	.212
QRS duration, ms	140 (110–164)	133.0 (110–161)	140 (110–164)	.313
Primary prevention ICD indication[b]	1299 (89.6)	184 (90.2)	1115 (89.6)	.782
CRT-D implanted[c]	1378 (74.9)	187 (70.6)	1191 (75.6)	.082
Ischemic cause of heart failure	895 (48.6)	151 (57.0)	744 (47.2)	.003
Hypertension	1171 (64.7)	163 (62.0)	1008 (65.2)	.312
Systolic blood pressure, mm Hg	120 (110–130)	120 (110–130)	120 (110–130)	.525
Valvular heart disease	1102 (65.7)	172 (70.2)	930 (64.9)	.106
Atrial fibrillation history	363 (21.8)	82 (33.9)	281 (19.7)	<.001
History of stroke or TIA	150 (9.6)	27 (12.7)	123 (9.2)	.105
Diabetes	667 (36.3)	104 (39.2)	563 (35.8)	.279
Renal insufficiency	350 (19.5)	75 (30.5)	275 (17.7)	<.001
Chronic pulmonary disease	284 (15.8)	51 (20.6)	233 (15.1)	.026
Liver disease	47 (3.7)	10 (6.1)	37 (3.4)	.080
Medication				
Beta blocker	1606 (88.5)	232 (87.9)	1374 (88.6)	.739
Diuretic	1591 (87.7)	251 (95.1)	1340 (86.4)	<.001
ACEI or ARB	1524 (84.0)	222 (84.1)	1302 (83.9)	.953
Antilipemic agent	944 (61.6)	128 (63.7)	816 (61.3)	.519
Antiplatelet	832 (45.9)	139 (52.9)	693 (44.7)	.014
Anticoagulant	585 (32.2)	113 (42.8)	472 (30.4)	<.001
Antiarrhythmic drug	387 (21.3)	70 (26.5)	317 (20.4)	.026
Digitalis	153 (8.4)	35 (13.3)	118 (7.6)	.002
Calcium antagonist	138 (7.8)	17 (7.0)	121 (7.9)	.612
Follow-up period, days	631 (385–865)	642 (378–941)	627 (385–856)	.864

Data are shown as median (interquartile range) or n (% of available data).
ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin receptor blocker; CRT-D = cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TIA = transient ischemic attack.
[a]Determined before device implantation except for "CRT-D implanted" and "Follow-up period."
[b]The remaining patients had secondary prevention indication.
[c]In addition, 4 patients with an ICD at baseline underwent upgrade to CRT-D during follow-up.

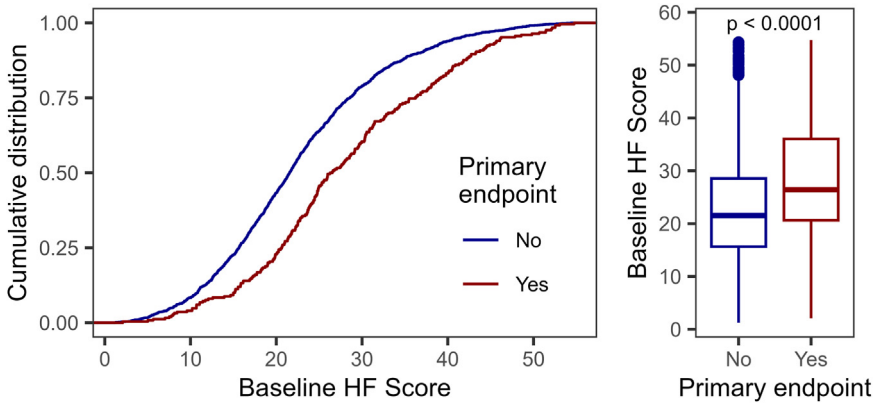

Figure 2
Empirical cumulative distribution function (*left*) and box plot (*right*) of baseline heart failure (HF) Score stratified by occurrence of the primary end point (composite of all-cause death or hospitalization for worsening HF). The plots show 95% of data after removal of outliers.

Figure 3 shows a significant distinction between Kaplan-Meier curves for high vs low baseline HF Score with respect to the primary end point (log-rank $P < .0001$), WHFH ($P < .0001$), all-cause death ($P < .0001$), and cardiovascular death ($P = .0012$). Sensitivity analysis performed by excluding SELENE HF data from the study pool provided consistent results (Supplemental Tables S3 and S4).

In the hierarchical event analysis of all-cause deaths as the outcome with highest priority and WHFHs as repeated event outcomes, the win ratio of low vs high score was 2.47 (95% CI, 1.89–3.24; $P < .0001$), consistent with the results of time-to-first-event analysis.

Discussion

In a pooled data set of 1841 patients with ICD or CRT-D device with atrial sensing capability observed for up to 5 years, a time-to-first-event analysis revealed that the baseline HF Score of the HeartInsight feature determined 97 days after the first remote monitoring message is associated with an increased long-term risk of WHFH and all-cause death, with a hazard ratio of 1.91–2.37 for high vs low score ($P \leq .0003$). The association was independent of the other adjusting covariates (AF history, renal insufficiency, ischemic cause, advanced age, NYHA class III, and diuretics use). The finding of the time-to-first-event analysis was also confirmed by the hierarchical analysis that included all-cause deaths as the event with major interest and all WHFHs as recurrent events, with a win ratio of 2.47 ($P < .0001$). The baseline HF Score was also associated with all-cause deaths, cardiovascular deaths, and WHFHs, in separate end point analyses.

By comparison, Botto and coworkers[3] have recently shown that the mean HF Score in patients with WHFHs reached a peak value of 52 ± 27 until the event but was already significantly higher (42 ± 26) 12 weeks before the event compared with the mean HF Score in control patients without WHFHs (31 ± 21). Of the 7 components of HeartInsight, 24-hour and night-time HR, HR variability, and thoracic impedance were the main drivers of the increased HF Score already 12 weeks before WHFHs, accounting for approximately 80% of the score value. Subsequently, all 7 algorithm components contributed to an additional increase in HF Score toward WHFHs, as necessary for alerts.[3] However, based on all these findings, we hypothesized that the HF Score in patients with WHFHs may be increased even before the time window of

Table 2 Univariable and multivariable analyses for the primary end point[a] and baseline HF Score as a continuous variable

	Univariable analysis		Multivariable analysis	
Covariate[b]	HR (95% CI)	*P* value	HR (95% CI)	*P* value
√ Baseline HF Score	1.03 (1.02–1.04)	**<.0001**	1.03 (1.02–1.04)	**<.0001**
Age (per year)			1.01 (1.00–1.03)	.07
√ AF history (yes vs no)			1.49 (1.08–2.05)	**.015**
NYHA (class III vs II)			1.27 (0.96–1.67)	.089
√ HF cause (ischemic vs other)			1.41 (1.07–1.85)	**.013**
√ Renal insufficiency (yes vs no)			1.48 (1.09–2.01)	**.013**
√ Diuretics (yes vs no)			1.94 (1.10–3.42)	**.022**

Boldface *P* values represent statistical significance; √, significant predictor in multivariable analysis.
AF = atrial fibrillation; CI = confidence interval; HF = heart failure; HR = hazard ratio; NYHA = New York Heart Association.
[a]Composite of all-cause death or hospitalization for worsening HF.
[b]Cox proportional hazards regression stratified by clinical trial: covariates were determined using the selection method of the stepwise procedure with the Akaike information criterion, among baseline HF Score, age, sex, body mass index, AF history, NYHA class, device type (cardiac resynchronization therapy defibrillator/implantable cardioverter-defibrillator), HF cause, renal insufficiency, chronic pulmonary disease, and use of diuretics and digitalis.

Table 3 Univariable and multivariable analyses for all end points and HF Score as a binary variable

	Univariable analysis		Multivariable analysis	
Covariate[a]	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Primary end point[b]				
√ Baseline HF Score (high vs low)[c]	2.22 (1.72–2.87)	**<.0001**	2.05 (1.54–2.71)	**< .0001**
Age (per year)			1.01 (1.00–1.03)	.12
√ AF history (yes vs no)			1.61 (1.17–2.20)	**.003**
NYHA (class III vs II)			1.27 (0.97–1.67)	.088
√ HF cause (ischemic vs other)			1.38 (1.05–1.81)	**.021**
√ Renal insufficiency (yes vs no)			1.47 (1.08–2.01)	**.014**
√ Diuretics (yes vs no)			1.98 (1.13–3.49)	**.018**
All-cause death				
√ Baseline HF Score (high vs low)[c]	2.72 (1.85–4.00)	**<.0001**	2.37 (1.56–3.58)	**<.0001**
Age (per year)			1.02 (1.00–1.04)	.087
√ AF history (yes vs no)			1.64 (1.06–2.56)	**.027**
NYHA (class III vs II)			1.08 (0.73–1.59)	.7
HF cause (ischemic vs other)			1.43 (0.96–2.13)	.076
√ Renal insufficiency (yes vs no)			1.68 (1.10–2.58)	**.017**
√ Diuretics (yes vs no)			2.52 (1.02–6.22)	**.046**
Hospitalization for worsening HF				
√ Baseline HF Score (high vs low)[c]	2.01 (1.47–2.74)	**<.0001**	1.91 (1.35–2.71)	**.0003**
Age (per year)			1.01 (0.99–1.03)	.29
√ AF history (yes vs no)			1.72 (1.16–2.55)	**.007**
NYHA (class III vs II)			1.34 (0.95–1.88)	.099
HF cause (ischemic vs other)			1.25 (0.89–1.75)	.2
Renal insufficiency (yes vs no)			1.45 (0.99–2.13)	.059
Diuretics (yes vs no)			1.77 (0.90–3.49)	.1
Cardiovascular death				
√ Baseline HF Score (high vs low)[c]	2.42 (1.35–4.34)	**.0031**	2.19 (1.14–4.22)	**.019**
√ Age (per year)			1.05 (1.01–1.09)	**.019**
AF history (yes vs no)			1.38 (0.69–2.76)	.36
NYHA (class III vs II)			0.74 (0.39–1.39)	.34
HF cause (ischemic vs other)			1.21 (0.65–2.25)	.55
Renal insufficiency (yes vs no)			1.80 (0.93–3.48)	.083
Diuretics (yes vs no)			2.8 (0.67–11.72)	.16

Boldface *P* values represent statistical significance; √, significant predictor in multivariable analysis.
AF = atrial fibrillation; CI = confidence interval; HF = heart failure; HR = hazard ratio; NYHA = New York Heart Association.
[a]Cox proportional hazards regression stratified by clinical trial.
[b]Composite of all-cause death or hospitalization for worsening HF.
[c]High >23, low ≤23, according to the cutoff determined by a time-dependent receiver operating characteristics curve analysis.

maximum 12 weeks used in that study, possibly already at "baseline" (ie, at algorithm activation simulated after 90 days of remote monitoring when the algorithm has been fed with full information). Findings of this study confirmed this hypothesis, showing that high HF Scores at baseline indicate worse initial conditions and could be used for baseline risk stratification relying only on device-monitored variables.

The HF Score of HeartInsight was developed for longitudinal short-term prediction of impending WHFHs during follow-up (for which it showed a C statistic of 0.89[1]) and not for long-term outcome (for which we expectedly obtained a lower C statistic of 0.63–0.65). Nevertheless, because both "baseline" and "week −12" high scores[3] were associated with an increased likelihood of major events, HeartInsight may be considered a tool reflecting the patient's condition or suboptimal treatment both at baseline and longitudinally in an automatic manner. This characteristic is particularly interesting compared with other risk stratifiers based on clinical parameters. The CHARMS,[11] GISSI-HF,[12] MAGGIC,[13] and SHFM[2] are well-known examples of accurate models predicting 1- to 5-year mortality in HF patients with either preserved or reduced LVEF, using 14–26 clinical parameters, including demographics, cause, comorbidity, blood/urine chemical test results, and therapy data. According to most recent data, these models achieved good prediction accuracy in all cases with a C statistic >0.70.[14] However, some limitations may hinder their widespread use on a routine basis. For meaningful projections, these models require several parameters that may not be available in all cases, may not be collected easily, or may be collected at different times. All parameters also need to be collected periodically to monitor the evolution of prognosis and the effect of treatments. Moreover, advancements in HF therapy or developments of novel drugs cannot be easily implemented in upgraded model versions, requiring complete revalidation.[15] The HF Score used in our analysis was based solely on variables monitored by implanted devices because the optional SHFM component of the algorithm was omitted. From this perspective, models

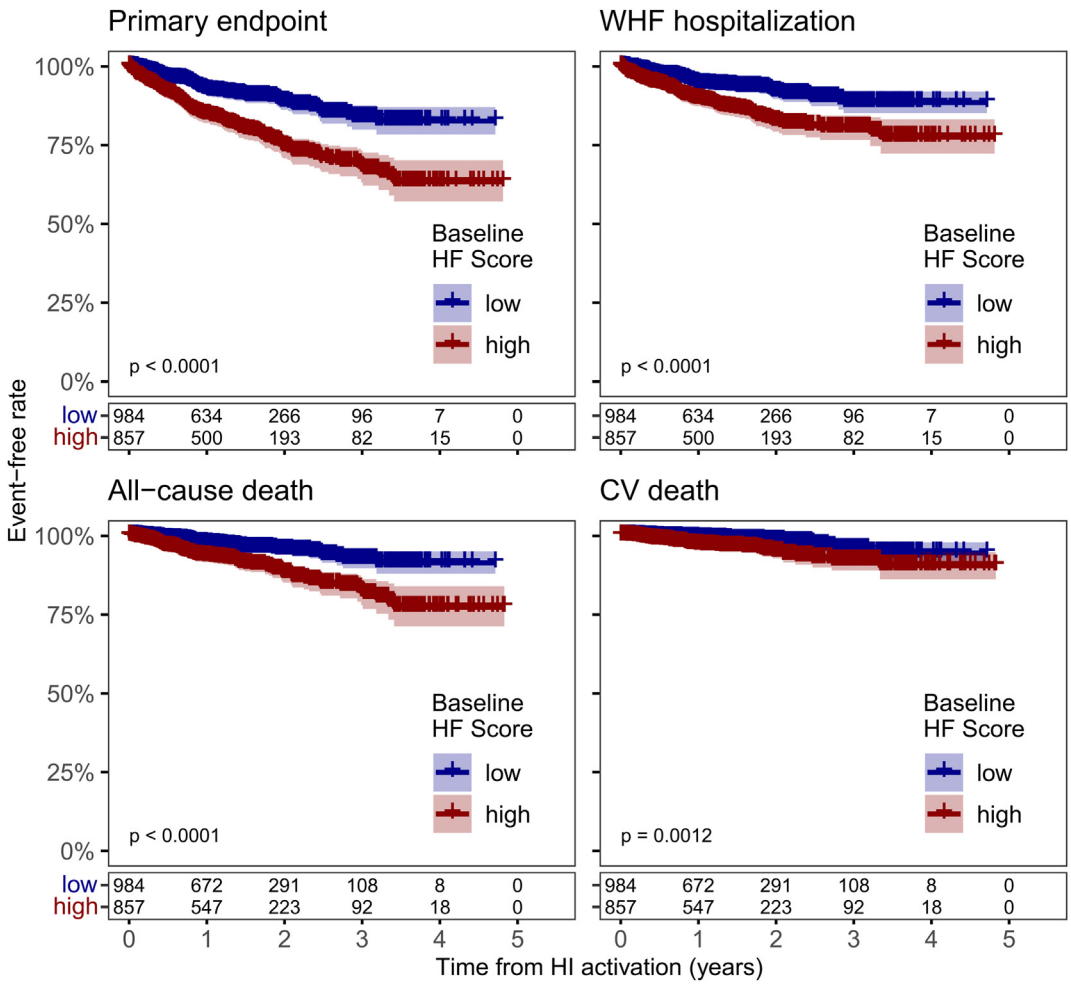

Figure 3

Kaplan-Meier plots comparing survival from the primary end point (composite of all-cause death or hospitalization for worsening heart failure [WHF]) and survival from secondary end points for high (>23) vs low (≤23) baseline heart failure (HF) Score according to the cutoff value determined by a time-dependent receiver operating characteristics curve analysis. The 95% confidence limits (*shaded areas*) and *P* values for the log-rank test are shown. CV = cardiovascular; HI = HeartInsight.

using device-collected physiologic parameters may have practical advantages, being continuously and automatically updated during follow-up and less prone to limitations relative to the introduction of new drugs or treatment strategies.[16]

During recent years, some multiparametric predictors based on device-collected information have been developed with the scope of warning of impending acute HF events.[17,18] They have been shown to be able to predict imminent WHFHs a few weeks in advance, but their association with long-term mortality has also been investigated lately. The maximum value of the Triage-HF Score (Medtronic, Minneapolis, MN) within the first 6 months from device implantation was collected to group patients with low, medium, and high risk and to compare mortality between groups in a database with >20,000 patients. High- and medium-risk patients had 3.5- and 1.8-fold increased mortality in a 2-year follow-up, respectively.[19,20] In a multicenter registry of 568 HF patients with reduced LVEF monitored with the HeartLogic algorithm (Boston Scientific, St Paul, MN), the mortality rate during in-alert periods was 10 times higher than in out-of-alert periods, with an adjusted hazard ratio of 9.2.[21] Similarly, in an analysis of a pooled data set of 9 trials, we showed that the HeartInsight HF Score calculated as a 7-day average after 90 days from the first remote monitoring transmission was significantly associated with an increased risk of WHFHs, all-cause death, and cardiovascular death. The group with high (>23) baseline HF Score had at least double risk compared with the group with low HF Score. However, the cutoff value of 23 for high vs low baseline HF Score, identified in the time-dependent ROC analysis, should not be generalized—first, because about 9.3% of patients in the low HF Score group still had a composite end point event of death or WHFH in 5 years. Second, the HeartInsight feature, like other multiparametric algorithms, has been developed to warn of imminent acute HF decompensation when the daily updated HF Score crosses a programmable threshold (45 default setting), not for long-term predictions. Third, the introduction of new therapies or drugs may affect estimation of the best cutoff of low vs high baseline HF Score. Nevertheless, the novel finding from our analysis indicates that patients with a higher baseline HF Score are associated with poorer prognosis or suboptimal treatment and therefore should be monitored more closely, including critical appraisal of medical therapy,

assessment of the patient's compliance, and avoidance of gaps in remote data transmissions,[22] delays in alert report reviews, and delays in response to findings.

Adoption of HeartInsight with baseline risk stratification according to our analysis may enable a more efficient use of health care resources for the management of HF patients. This may imply specific in-clinic workflows favoring multidisciplinary approaches as also recommended by guidelines.[23,24] Zanotto and Capucci[25] have recently discussed how to integrate these tools into the clinical workflow by proposing organizational models and shared guidance for the management of HF alerts. However, little is known about best models of integration into routine practice and, above all, whether all this translates into improved patient symptoms and outcomes. Comparative evidence is necessary to warrant large adoption of longitudinal multiparametric predictors.

Study limitations

In this retrospective analysis of 9 clinical trials, a broad period between 2008 and 2022 was covered, encompassing important advances in HF therapy and HF management over time (eg, the introduction of sodium-glucose cotransporter 2 inhibitors and mineralocorticoid receptor antagonists) and leading to certain heterogeneity in the final set of analyzed patients and in the pool of end point events. In addition, differences in data collection methods between studies resulted in the exclusion of many patients (as explained before) or in missing data. This heterogeneity of the pooled data sets supports the generalizability of results, although the exclusion of most of the pooled cohort (albeit due to selection criteria unrelated to the analysis objectives) remains a limitation. Cardiovascular mortality may be underestimated in our analysis because in 11 of 122 deaths (9%), the cause could not be determined or was not reported. In addition, the history of WHFHs before study enrollment and N-terminal pro–B-type natriuretic peptide values were not collected in all studies, and their association with the HeartInsight HF Score could not be investigated. The proarrhythmic effect of digitalis[26] that was used in 13% of patients with a primary end point event may have negatively interfered with survival in this group.

The HeartInsight's HF Score computation is designed to detect conditions potentially leading to WHF in the short term during remote monitoring. Our results do not support its use as a model for accurate mortality projections in the long term. We determined the average HF Score at baseline, which is different from the HF Score as such. Nevertheless, a high value of the (daily) HF Score at baseline may help identify patients who are at higher risk at subsequent follow-up and require more attention than patients with low baseline HF Scores.

Following the manufacturer's instructions for the use of HeartInsight, patients with long-standing persistent or permanent AF, LVEF >35%, or NYHA class other than II/III at study enrollment were excluded from the analysis, although they can be encountered in clinical practice. NYHA class IV was excluded as it may involve clinical instability associated with acute decompensation and be linked with high mortality rates. Our results show an association between higher baseline HF Scores and worse prognosis in CRT-D/ICD patients before progression to the most severe class of HF symptoms, highlighting the potential role of baseline HF Score as an early risk stratifier.

AF ablation procedure before study enrollment was not an exclusion criterion and the corresponding data were not collected systematically. Moreover, 26 patients from the CASTLE-AF trial who underwent AF ablation after enrollment were included in the analysis and constitute 1.4% of the patient cohort. Regardless of AF ablation status, history of AF was one of the most important covariates in our survival models.

Conclusion

This study confirmed the hypothesis that high baseline HF Scores based only on device-monitored variables indicate worse initial clinical conditions. The mean HF Score of HeartInsight at baseline may serve as a risk stratifier to distinguish between patients at higher or lower long-term risk of all-cause death or WHFH.

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Appendix
Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2024.10.005.

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