openheart

Evaluating an alert-based multiparametric algorithm for predicting heart failure hospitalisations in patients with implantable cardioverter-defibrillators: a meta-cohort study

Alan Bulava,[1] João De Sousa,[2] Laurence Guédon-Moreau,[3] Morio Shoda,[4] Tobias Timmel,[5] Sally Thompson Hilpert,[5] Antonio D'Onofrio[6]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/openhrt-2025-003474).

To cite: Bulava A, De Sousa J, Guédon-Moreau L, *et al*. Evaluating an alert-based multiparametric algorithm for predicting heart failure hospitalisations in patients with implantable cardioverter-defibrillators: a meta-cohort study. *Open Heart* 2025;**12**:e003474. doi:10.1136/openhrt-2025-003474

Received 5 June 2025
Accepted 10 June 2025

For numbered affiliations see end of article.

Correspondence to
Dr Alan Bulava; alanbulava@seznam.cz

ABSTRACT

Background The alert-based HeartInsight algorithm predicts risk of worsening heart failure hospitalisations (WHFHs) by evaluating temporal trends of seven physiologic parameters obtained through automatic daily remote monitoring of implantable cardioverter-defibrillators. The aim of the present study was to evaluate the predictive performance of HeartInsight in a larger and more heterogeneous meta-cohort of patients, incorporating newer device generations and including patients managed with the most recent guideline-directed medical therapy (GDMT).

Methods The HeartInsight algorithm was retrospectively applied to data from four clinical trials in which WHFH events were adjudicated by independent external boards and remote monitoring was activated to provide relevant parameter trends. The analysis comprised 1352 patients with New York Heart Association (NYHA) class II/III, and no long-standing atrial fibrillation.

Results During a median follow-up of 599 days, 110 patients (median age 68 years (IQR, 61–75), 75.7% male) had a total of 165 WHFHs. The estimated sensitivity of WHFH prediction, as determined by generalised estimating equations, was 51.5% (95% CI 43.0% to 59.9%). The false alert rate was 0.85 per patient-year, the median alerting time was 34 days (IQR, 16–78) and the specificity was 81.4% (95% CI 80.4 to 82.4%). The results were verified in the multivariable analysis with two adjusting covariates (newer/older device generation and quadruple/other GDMT) and in the univariable analysis of prespecified patient subgroups according to NYHA class, aetiology and sex, showing no significant differences.

Conclusions Study results underscore the robustness of the predictive algorithm in a heterogeneous and contemporarily managed heart failure population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The alert-based HeartInsight algorithm is designed to predict worsening heart failure hospitalisations by evaluating seven temporal trends of physiologic parameters obtained through automatic daily remote monitoring of implantable cardioverter-defibrillator and cardiac resynchronisation therapy defibrillator recipients. The algorithm was developed and internally validated in the Selection of Potential Predictors of Worsening Heart Failure (SELENE HF) study.

WHAT THIS STUDY ADDS

⇒ We verified the predictive performance of HeartInsight in a larger and more heterogeneous meta-cohort of patients pooled from four clinical trials, incorporating newer device generations and including patients managed with the most recent guideline-directed medical therapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Study results are consistent with the SELENE HF validation and indicate the robustness of the algorithm to predict worsening heart failure (HF) hospitalisation risk in a heterogeneous and contemporarily managed HF patient population.

INTRODUCTION

Despite treatment improvements, worsening heart failure (WHF) is still associated with a poor prognosis and high rates of costly unplanned rehospitalisations.[1 2] Early clinical intervention for WHF events is a key strategy to delay disease progression, improve patient outcomes and reduce management costs.[3] HeartInsight (Biotronik SE & Co. KG, Berlin, Germany) is an alert-based feature designed to predict high risk of WHF events by evaluating temporal trends of physiologic parameters obtained through automatic daily remote monitoring of implantable cardioverter-defibrillators (ICDs) and cardiac resynchronisation therapy defibrillators (CRT-Ds).[4] The HeartInsight algorithm was developed and internally validated in the Selection of Potential Predictors of Worsening Heart Failure

(SELENE HF) study. The algorithm can be optionally combined with a baseline patient risk profile (the Seattle HF Model (SHFM)).[4 5] With default algorithm settings, the sensitivity of HeartInsight in predicting the first post-implant WHF hospitalisation (WHFH) was 65.5%, and the false alert rate was 0.69 per patient-year (one false alert every 17.4 months).[4] For the combined endpoint of any WHFH, outpatient intravenous interventions, or death related to WHF, the sensitivity was 54.8% and the false alert rate 0.67 per patient-year.[4]

We pooled data from four clinical trials to evaluate the algorithm's diagnostic performance in predicting WHFH events in a larger and more heterogeneous meta-cohort of patients, incorporating newer device generations and more recent approaches to HF management.

METHODS

The HeartInsight algorithm was retrospectively applied to clinical and remote monitoring data from completed or ongoing prospective trials in which WHF events were adjudicated by independent external boards and Biotronik Home Monitoring (HM) was activated to provide relevant parameter trends in devices that are now HeartInsight-marketed or are technically equivalent (Iforia/Ilesto/Idova series and successors). The optional SHFM score was not used in our analysis since the input data were not available in all studies. At the time of these studies, the HeartInsight algorithm was under development and not available to the investigators.

Patients from the included studies contributed to the present analysis if they had a New York Heart Association (NYHA) class II or III before device implantation, had no long-standing or permanent atrial fibrillation and had received an CRT-D or ICD device capable of atrial sensing (a dual-chamber ICD or a 'DX ICD' with a floating atrial dipole on the ICD lead,[6] with thoracic impedance feature programmed 'on' and with active HM). These are mandatory requirements for the computation of the algorithm and for the utilisation of HeartInsight according to its instructions of use.

HeartInsight algorithm

Recently integrated into the HM platform, HeartInsight calculates a heart failure (HF) score daily by evaluating temporal trends of seven longitudinal HM parameters collected during the preceding 90 days: 24-hour heart rate, nocturnal heart rate, heart rate variability, atrial tachyarrhythmia, ventricular extrasystoles, physical activity and thoracic impedance.[4 7] When this score, termed 'HF Score', exceeds a programmable nominal threshold (default setting: 45) for 3 consecutive days, the system alerts clinical staff to an increased risk of WHFH by a standard HM notification and provides all relevant HF diagnostics.[7] The alert status is terminated when the HF Score falls below a recovery threshold (10 points below the nominal threshold). The nominal threshold is then re-established as a criterion to trigger a new alert.[7]

WHF hospitalisations

In this study, adjudicated WHFHs were defined as non-elective hospital admissions with at least one overnight stay triggered by symptoms, signs or objective evidence of WHF as the primary cause of admission and in addition requiring the administration of intravenous therapy for HF, such as diuretics, vasodilators, or inotropic agents.[7]

Study methods

The first and any recurrent WHFH occurring ≥30 days post implantation (after the algorithm run-in period) and associated with at least 55% of days with HM transmissions within 90 days prior to a WHFH event were endpoints ('usable events') in this analysis. The 55% cut-off for the HM transmission rate is used by HeartInsight to ensure sufficient input information even with moderate HM compliance.[4]

We determined sensitivity based on endpoint events preceded by a true-positive alert. An alert was considered true positive if the HF Score did not fall below the recovery threshold between alert and event. Alerting time is defined as the number of days between a true-positive alert and ensuing event. Specificity was calculated based on the percentage of days with HF Score values appropriately below nominal threshold. False alert rate was the number of alerts not followed by WHFH, averaged per patient-year. Adjusting covariates for sensitivity and specificity estimates were the device generation (latest Acticor/Rivacor and Ilivia Neo/Intica Neo families vs predecessors) and the HF guideline-directed medical therapy (GDMT) at baseline (quadruple therapy vs triple therapy or less).[8]

All calculations were performed post hoc using default algorithm settings and prospectively collected HM data and clinical endpoint data. Patients who were lost to follow-up or died contributed to the analyses up to the date of last available information. For ongoing trials, the database was locked on 17 January 2024. To achieve the most complete information on source data and adjudication outcomes, hospitalisation details were updated, and event adjudications were provided until 25 November 2024.

To explore HeartInsight performance under specific patient conditions, the analysis was repeated in prespecified subgroups based on selected baseline characteristics: NYHA class (II vs III), device type (ICD vs CRT-D), HF aetiology (ischaemic vs non-ischaemic) and biological sex (female vs male), factors that may influence risk of worsening HF.[9–12]

Statistical analysis

Generalised estimating equations (GEE) were used to model the within-patient correlation of repeated measurements, including WHF events and follow-up days. To estimate sensitivity, a GEE model with a binomial family distribution was applied. The structure of the correlation matrix was tested using both independence and first-order autoregressive settings. The optimal structure was selected based on the correlation information criterion and was consistently applied to all subsequent GEE calculations.

The impact of adjusting covariates on sensitivity and specificity was examined using a multivariable GEE model. For prespecified subgroup comparisons of sensitivity, specificity and alerting time, a univariable GEE model was employed along with the Wald test. The family distribution for alerting time was set to Gaussian. Estimates of sensitivity and specificity are reported with 95% CI.

Continuous variables are reported as median with IQR. Binary or categorical variables are reported as counts and percentages of non-missing data. In all cases, a p value <0.05 was considered statistically significant. The analysis was performed with *R* statistical software (V.4.3.0; R Core Team 2023, https://www.R-project.org), and GEE was modelled using the R package glmtoolbox.

Patient and public involvement

Patients and/or public were not involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

Patients

One ongoing (BIO|Stream.HF)[13] and three completed trials (DetectICI, ECOST-CRT[14] and validation cohort of SELENE HF)[4] met the study inclusion criteria. Online supplemental table S1 summarises essential characteristics of these trials. In the pooled cohort, we identified 1352 patients fulfilling the prespecified eligibility criteria. Online supplemental table S2 shows that 80.8% of the patients came from trials other than SELENE HF, mainly from BIO|Stream.HF, which contributed 55.6% of all patients.

There was a relatively broad geographical distribution of patients (80% Europe, 17% Asia, 2% Oceania and 1% Africa, see online supplemental table S2 footnote). Patient characteristics at baseline are summarised in table 1. The median patient age was 68 years (IQR, 61–75 years), and three quarters were male (75.7%). NYHA class II (54.5%) slightly prevailed over class III (45.5%). The median left ventricular ejection fraction was 30% (IQR, 25%–33%). Nearly half of the patients (47.6%) had HF of ischaemic aetiology. In terms of medication, 90.8% of patients were taking an angiotensin-converting enzyme inhibitor, an adenosine receptor blocker or an angiotensin receptor neprilysin inhibitor; 86.3% were on beta blockers; and 54.9% were using mineralocorticoid receptor antagonists. Some recent patients (17.9% of all) were also taking sodium-glucose cotransporter 2 (SGLT2) inhibitors.

All patients in BIO|Stream.HF, DetectICI and ECOST-CRT trials, and 103 SELENE HF patients received a CRT-D (88.4% of all patients), 110 SELENE HF patients received conventional dual-chamber ICD (8.1% of all

Table 1 Baseline characteristics of 1352 patients included in the present study

Parameter*	Value
Age, years	68 (61–75)
Male sex	1024 (75.7)
Body mass index, kg/m^2	27 (24.1–30.5)
New York Heart Association class	
II	737 (54.5)
III	615 (45.5)
LVEF, %	30 (25–33)
QRS duration, ms	153 (130–170)
Primary prevention ICD indication†	1063 (86.2)
Ischaemic heart failure aetiology	643 (47.6)
Hypertension	867 (64.2)
Systolic blood pressure	120 (110–134)
Atrial fibrillation history	330 (24.4)
History of stroke or TIA	119 (8.8)
Diabetes	516 (38.2)
Chronic renal insufficiency	275 (20.3)
Chronic obstructive pulmonary disease	208 (15.4)
Implanted device type	
CRT-D	1195 (88.4)
Dual-chamber ICD	110 (8.1)
Single-lead ICD with atrial sensing (DX ICD)	47 (3.5)
Implanted device generation	
Latest‡	617 (45.6)
Previous generations	735 (54.4)
Medication	
ACEI, ARB or ARNI	1134 (90.8)
Beta-blocker	1149 (86.3)
Mineralocorticoid receptor antagonist	731 (54.9)
SGLT2 inhibitor	239 (17.9)
Quadruple guideline-directed medical therapy§	161 (12.1)
Diuretic	963 (72.4)
Antilipemic agent	836 (62.8)
Antiplatelet	678 (50.9)
Anticoagulant	464 (34.9)
Antiarrhythmic drug	293 (22)
Ca^{2+} antagonist	126 (9.5)
Digitalis	51 (3.8)

Data are shown as median (IQR) or n (% of available data).
*Determined before device implantation except for 'Implanted device'.
†The remaining patients had secondary prevention indication.
‡Acticor/Rivacor/Ilivia Neo/Intica Neo families.
§Prescription of all four medication categories listed above.
ACEI, angiotensin-converting-enzyme inhibitor; ARB, adenosine receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CRT-D, cardiac resynchronisation therapy defibrillator; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; SGLT2, sodium-glucose cotransporter 2; TIA, transient ischaemic attack.

Table 2 GEE results when exploring different settings for the structure of the correlation matrix

Matrix correlation structure	Sensitivity		Specificity
	Estimate, % (95% CI)	Correlation information criterion	Estimate, % (95% CI)
Independence	51.7 (43.2 to 60.2)	1.08260	81.0 (80.0 to 82.0)
Auto-regressive first order	51.5 (43.0 to 59.9)	1.07224	81.4 (80.4 to 82.4)

GEE, generalised estimating equations.

patients) and 47 SELENE HF patients received a DX ICD (3.5% of all patients). In 617 (45.6%) patients, a device of the latest generation was implanted.

Follow-up and WHFHs

During a median follow-up of 599 days (IQR, 360–899 days), 110 patients (8.1%) had a total of 165 WHFHs, of which 145 hospitalisations (87.9%) met the prespecified endpoint criteria. The general WHFH rate ranged from 4.1 (BIO|Stream.HF trial) to 14.7 (DetectICI trial) per 100 patient-years, with an average rate of 6.6 WHFHs per 100 patient-years. Twenty WHFH events were deemed unusable: 10 occurred before the run-in period ended and the remaining 10 were associated with <55% of days with HM transmissions in 90 days preceding the event.

The median HM transmission success rate during the follow-up of 1352 patients was 95.3% (IQR, 87.3%–98.8%).

HeartInsight predictive performance

The estimated sensitivity of HeartInsight for predicting WHFHs at its default settings, as determined by GEE, was 51.5% (95% CI 43.0 to 59.9%), and with the independence setting of the correlation structure, it was 51.7% (95% CI 43.2 to 60.2%). According to the correlation information selection criterion, the autoregressive structure yielded the best results (table 2). With this setting, the specificity estimate was 81.4% (95% CI 80.4 to 82.4%). The false alert rate was 0.85 per patient-year and the median alerting time, also called lead time, was 34 days (IQR, 16–78 days) (table 3).

Subgroup analysis

In the multivariable analysis, none of the two adjusting covariates had a significant effect on either sensitivity (quadruple therapy, p=0.21; device generation, p=0.15) or specificity (quadruple therapy, p=0.22; device generation, p=0.96).

In the univariable analysis, differences between subgroups were not statistically significant (all p values >0.10). Sensitivity and median alerting time ranged from 46.1% (NYHA class II) to 56.8% (NYHA class III) and from 29 (ischaemic) to 45 days (non-ischaemic aetiology), respectively (table 3, figure 1). Specificity and false positive alert rate ranged from 81.0% (male) to 82.8% (female sex) and from 0.80 (female sex) to 0.88 alerts per patient-year (non-ischaemic).

DISCUSSION

The diagnostic performance of the HeartInsight algorithm, initially validated in the SELENE HF trial,[4] is further evaluated in this study at the default nominal

Table 3 HeartInsight performance at a default nominal alert threshold of 45: univariable analysis

Patient group	Pts (n)	WHFHs (n): predicted/usable	Sensitivity of prediction (%)	Alerting time (days)	FP rate (ppy)	Specificity of prediction (%)
All patients	1352	75/145	51.5 (43.0–59.9)	34 (16–78)	0.85	81.4 (80.4–82.4)
Subgroups						
NYHA II	737	26/59	46.1 (32–60.3)	31 (14–80)	0.86	81.1 (79.7–82.4)
NYHA III	615	49/86	56.8 (47.2–66.5)	36 (17–78)	0.84	81.9 (80.5–83.3)
P value for NYHA	–	–	0.21	0.50	–	0.39
Ischaemic	643	47/84	55 (43.8–66.3)	29 (14–78)	0.82	81.5 (79.9–83.0)
Non-ischaemic	709	28/61	46.4 (33.9–58.9)	45 (19–89)	0.88	81.4 (80.1–82.7)
P value for aetiology	–	–	0.32	0.89	–	1.00
Female	328	18/36	50 (35.6–64.4)	41 (16–64)	0.80	82.8 (80.9–84.6)
Male	1024	57/109	52.8 (42.7–62.8)	33 (16–81)	0.87	81.0 (79.8–82.1)
P value for sex	–	–	0.59	1.00	–	0.13

Data are shown as counts, percentages [95% CIs], median (interquartile ranges) or values.
FP, false positive; NYHA, New York Heart Association class; ppy, per patient-year; pts, patients; WHFH, worsening heart failure hospitalisation.

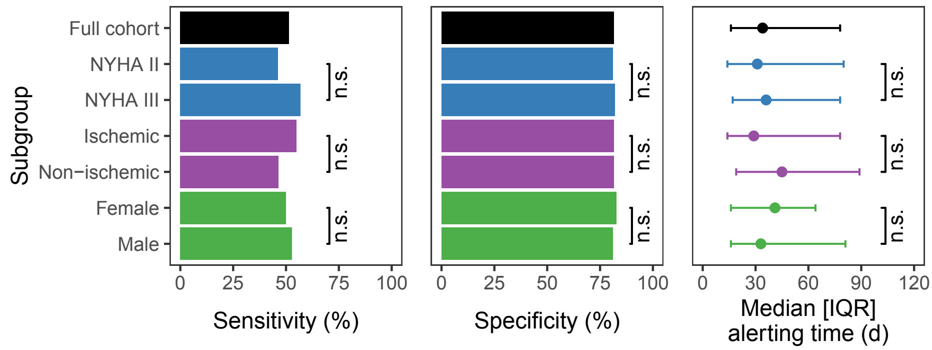

Figure 1 HeartInsight sensitivity, specificity and alerting time across patient subgroups from table 3, using a default nominal alert threshold of 45. For each subgroup comparison, the level of significance is indicated. d, days; n.s., not significant; NYHA, New York Heart Association class.

threshold and within a more heterogeneous and larger patient cohort, incorporating newer device generations and more recent pharmacotherapy for HF management. The sensitivity to predict any WHFH event is estimated to be 51.5%, with a median alerting time of 34 days and a false alert rate of 0.85 per patient-year. This is the first analysis to explore the sensitivity and specificity parameters of HeartInsight in patients with a subset managed under current GDMT and in key subgroups with varying risk profiles for WHFH events.

The analysis suggests that HeartInsight can predict WHFH events across various patient subgroups, including sex, NYHA class, device type and HF aetiology. Although there were slight differences in subgroup comparisons, these were not significant in the univariable analysis. Of note, the subgrouping by device type was considered of limited relevance due to the low number of patients with an ICD without cardiac resynchronisation therapy option. The original validation of the algorithm in the SELENE HF trial included a significant proportion of ICD patients (56.4%),[4] but only SELENE HF contributed ICD patients to the present meta-cohort.

Our reported median HM transmission success rate exceeding 95% corresponds to an average of one unsuccessful transmission every 20 days. This high transmission rate is consistent with findings across a wide range of Biotronik HM studies,[6 15 16] suggesting that clinicians can rely on receiving daily updated HeartInsight data via the Biotronik HM system.

Comparison with SELENE HF results

There are differences between the present evaluation and the validation during the development of the algorithm. First, the primary endpoint chosen in the initial validation analysis was the first post-implant WHFH,[4] whereas the endpoint chosen for this analysis was any WHFH, to better reflect routine clinical practice.

Second, the optional SHFM score could not be included in this analysis. However, the impact of the SHFM score omission on the outcome is expected to be minimal. By comparison, in the SELENE HF trial, the SHFM score did not influence the sensitivity (65.5%), but only the false alert rate (improved from 0.76 to 0.69/patient-year with SHFM) and the median alerting time (reduced from 62 to 42 days with SHFM).[4]

The sensitivity of 51.5% in the present analysis is comparable to the sensitivity of 54.8% for the secondary endpoint in SELENE HF, which was largely driven by any WHFH (as in the present analysis) and not exclusively by the first WHFH.[4] The secondary endpoint in SELENE HF also included outpatient intravenous interventions for acute HF and deaths related to WHF, but these events were infrequent, accounting for less than 20% of the secondary endpoints in the SELENE HF validation cohort.[4]

The false alert rate of 0.85 per patient-year (one false alert every 14.1 months) in our meta-cohort of patients is comparable with the false alert rate of 0.67 for the secondary endpoint (one false alert every 17.9 months) in the SELENE HF trial, at the nominal threshold of 45.[4] As mentioned above, this moderately higher value can be partly explained by the omission of the SHFM score.

The alerting time of 34 days in the present analysis is similar to the 43 days (secondary endpoint) in SELENE HF.[4] The specificity was slightly reduced from 86.5% (SELENE HF) to 81.4% in the current analysis.

Overall, similar results were obtained in this larger and more heterogeneous patient meta-cohort, incorporating newer device generations and more recent approaches to HF management, as in the SELENE HF trial that was the basis for the development and validation of the HeartInsight algorithm. This is noteworthy, given the expectation that the predictive performance of new algorithms in larger and more diverse patient populations will typically be slightly lower than the original internal validation values.[17 18] With newer device generations, there are typically minor improvements made to the software, and it was considered relevant to confirm that these changes did not impact the algorithm performance. Therefore, the results of the present meta-cohort study are consistent with expectations.

It is important to recognise that sensitivity, false alert rate and specificity should not be considered intrinsic characteristics of the HeartInsight algorithm, as they depend on the programmable nominal threshold used for calculations. The default setting of the nominal threshold (45) favours a low false alert rate and high specificity. It is possible, however, to change the default alert threshold to increase sensitivity, at the expense of an acceptable increase in false alert rate. For instance, the Selene HF study reported a sensitivity of 64.5% and a false alert rate of 1.05 per patient-year for the combined endpoint of recurrent WHFHs or death using a nominal threshold of 35.

Furthermore, in the initial validation analysis for HeartInsight, an alert was classified as true positive if the index did not fall below the recovery threshold between the alert and an event. It is worthy of note that the different algorithms available have been developed based on varying definitions of a true-positive alert. For example, with HeartLogic, the sensitivity estimate included alerts that reset within a 30-day period prior to an event.[19] These different definitions limit the extent to which the sensitivity and specificity can be compared.

General discussion

The studies included in the present analysis were limited to those in which WHFH events had been adjudicated as primary events by an external assessment board, so a strict definition of WHFH was applied. In clinical practice, for hospitalisation events related to WHF, it can be challenging for clinicians to distinguish between primary and secondary events. Patients with HF often have multiple comorbidities that predispose them to WHF events and adverse social factors can compound an unfavourable prognosis.[20] Therefore, algorithms such as HeartInsight may in practice detect more events associated with WHF than the primary endpoint of this analysis suggests—a topic that needs to be explored in future studies.

The WHFH rate in our meta-cohort was 6.6 per 100 patient-years and most of the WHF events included in our analysis were first post-implant WHFH events. In an individual patient, the risk of WHFH typically increases over time and as the disease progresses[21] and is higher in the period following an event.[22] In device patients, WHFH rate can vary significantly depending on existing standards of cardiology care and patient characteristics such as comorbidity profiles, time since HF diagnosis and device implantation, and previous WHF events.[23] If basic remote monitoring services are well established, reported WHFH rates are likely to be lower than in patients managed in clinics without such a service.[15] Patients included in the meta-cohort were remotely monitored and primarily enrolled after denovo device implantation.

The pooled patient cohort was based on four clinical studies and included 1352 patients, most of whom were implanted with a CRT-D device. Three of the four studies were completed prior to the most recent European Society of Cardiology guidelines update that suggested the extension of foundational HF therapy to include SGLT2 inhibitors.[8] But, in the ongoing BIO|Stream.HF observational registry, a subset of patients used a quadruple foundational therapy. Therefore, 161 (11.9%) out of 1352 patients in our study were on this expanded medication regimen at baseline, and 239 (17.7%) patients were using an SGLT2 inhibitor. Our results suggest that the inclusion of patients treated with up-to-date HF medication has no clinically relevant impact on the predictive performance of HeartInsight. Likewise, we found no significant impact on the predictive performance of HeartInsight using latest device generations.

Although diagnostic performance is an important aspect of the utility of an alert-based WHF risk monitoring strategy, technology alone is clearly not sufficient to improve patient outcomes. Solutions such as HeartInsight need to be integrated appropriately and efficiently into routine clinic workflow, and patients need to be followed up in a timely manner after an alert, so that appropriate action can be taken, when necessary.[24] This present analysis is retrospective and designed to address prediction of WHFH events. The next step is to test whether early prediction in centres with integrated remote monitoring capabilities, with appropriate intervention, can prevent WHF events, leading to hospitalisation or other urgent care and deterioration in health-related quality of life.

Study limitations

Exclusion of patients from the pooled patient cohort due to inclusion/exclusion criteria may be a potential source of bias. A further limitation of the present analysis relates to the differences in foundational medication over time, as only a minority of patients received the most recent optimal GDMT. There was also some inconsistency in reporting baseline data, such as comorbidities and medication, among the included trials. A further limitation was that highly selected endpoint (WHFH) events do not fully reflect the real-world situation since secondary HF events and events managed in an outpatient setting were not considered. In addition, the event rate in the ongoing BIO|Stream.HF trial may be underestimated due to possibly not yet complete source documentation or events pending board adjudication. Finally, the subgroup analysis by device type was of limited relevance since only one study (SELENE HF) contributed ICD devices to the pooled data.

CONCLUSIONS

In conclusion, this analysis has evaluated the diagnostic performance of the HeartInsight algorithm in a larger, heterogeneous cohort of HF patients receiving contemporary pharmacotherapy. Sensitivity without the contribution of the SHFM score was estimated to be greater than 50% for a primary WHFH event, with a median alerting time of more than 4 weeks and a false alert rate of less than one per patient-year of follow-up. These results are consistent with the initial SELENE HF validation and underscore the robustness of the HeartInsight algorithm in HF patients implanted with devices with ICD capabilities.

Author affiliations
[1]Ceske Budejovice Hospital, University of South Bohemia in Ceske Budejovice, Ceske Budejovice, Czech Republic
[2]Cardiology, Unidade Local de Saúde de Santa Maria, EPE, Lisboa, Portugal
[3]CHU Lille, Lille University Hospital Center, Lille, France
[4]Department of Cardiology, Tokyo Women's Medical University, Tokyo, Japan
[5]BIOTRONIK SE & Co KG, Berlin, Germany
[6]Unità Operativa di Elettrofisiologia, Studio e Terapia delle Aritmie, Monaldi Hospital, Naples, Italy

Acknowledgements The authors are thankful to Sara Ciucci and Bernd Bruesehaber for statistical analysis, Dejan Danilovic for medical writing assistance, and Alessio Gargaro and Hans-Jörg Sommerlade for critical review of the manuscript.

Contributors AB formulated the initial ideas and research questions, outlined the draft of the manuscript along with its revisions, and supervised the research, including data collection. JdS, LG-M and MS developed and refined the research methods while also collecting data. TT and STH organised, stored and prepared the data for analysis, in addition to revising the manuscript. Furthermore, they managed project resources, finances and logistics. TT, STH and ADO performed statistical analyses of the data, interpreted the results and drew conclusions. All authors engaged in discussions about the results, provided feedback, and critically reviewed, edited and revised the manuscript. Guarantor: AB.

Funding The study was supported by Biotronik SE & Co KG (Woermannkehre 1, D-12359 Berlin, Germany).

Competing interests AB received consultant fees and/or grant support from Abbott, Biotronik, and Boston Scientific. JDS received grant support and/or consultant fees from Microport and Medtronic outside the submitted work. MS received grant support from Abbott, Biotronik, Boston Scientific, and Medtronic. LG-M received fees for lectures and/or consulting from Novartis, Microport, Boston Scientific, and Medtronic outside the submitted work. Lille University Hospital Center received grants from BMS, Abbott, Biotronik, Boston Scientific, Microport and Medtronic outside the submitted work. TT and STH are employees of Biotronik SE & Co. KG, Berlin, Germany.

Patient consent for publication Not applicable.

Ethics approval The present analysis did not require ethical approval. All studies included conform with the principles outlined in the Declaration of Helsinki and were approved by the relevant national and local ethics committees. All patients gave written informed consent to participate in the studies.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available upon reasonable request. The data underlying this article were provided by Biotronik SE & Co KG. Data will be shared upon reasonable request to the corresponding author with the permission of Biotronik SE & Co KG.

ORCID iD
Alan Bulava http://orcid.org/0000-0002-1742-207X

REFERENCES

1 Samsky MD, Ambrosy AP, Youngson E, *et al*. Trends in Readmissions and Length of Stay for Patients Hospitalized With Heart Failure in Canada and the United States. *JAMA Cardiol* 2019;4:444–53.
2 Givertz MM, Yang M, Hess GP, *et al*. Resource utilization and costs among patients with heart failure with reduced ejection fraction following a worsening heart failure event. *ESC Heart Fail* 2021;8:1915–23.
3 Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol* 2016;13:368–78.
4 D'Onofrio A, Solimene F, Calò L, *et al*. Combining home monitoring temporal trends from implanted defibrillators and baseline patient risk profile to predict heart failure hospitalizations: results from the SELENE HF study. *EP Europace* 2022;24:234–44.
5 Levy WC, Mozaffarian D, Linker DT, *et al*. The Seattle Heart Failure Model. *Circulation* 2006;113:1424–33.
6 Hindricks G, Theuns DA, Bar-Lev D, *et al*. Ability to remotely monitor atrial high-rate episodes using a single-chamber implantable cardioverter-defibrillator with a floating atrial sensing dipole. *Europace* 2023;25:euad061.
7 Botto GL, Sinagra G, Bulava A, *et al*. Predicting worsening heart failure hospitalizations in patients with implantable cardioverter defibrillators: is it all about alerts? A pooled analysis of nine trials. *Europace* 2024;26:euae032.
8 McDonagh TA, Metra M, Adamo M, *et al*. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42:3599–726.
9 Lindberg F, Lund LH, Benson L, *et al*. Trajectories in New York Heart Association functional class in heart failure across the ejection fraction spectrum: data from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2022;24:2093–104.
10 Zeitler EP, Austin AM, Leggett CG, *et al*. Complications and Mortality Following CRT-D Versus ICD Implants in Older Medicare Beneficiaries With Heart Failure. *JACC: Heart Failure* 2022;10:147–57.
11 Martens P, Nijst P, Verbrugge FH, *et al*. Profound differences in prognostic impact of left ventricular reverse remodeling after cardiac resynchronization therapy relate to heart failure etiology. *Heart Rhythm* 2018;15:130–6.
12 Leyva F, Qiu T, Zegard A, *et al*. Sex-Specific Differences in Survival and Heart Failure Hospitalization After Cardiac Resynchronization Therapy With or Without Defibrillation. *J Am Heart Assoc* 2019;8:e013485.
13 Schmitt J, Wenzel B, Brüsehaber B, *et al*. Impact of lockdown during COVID-19 pandemic on physical activity and arrhythmia burden in heart failure patients. *Pacing Clinical Electrophis* 2022;45:471–80.
14 Klein C, Kouakam C, Lazarus A, *et al*. Comprehensive vs. standard remote monitoring of cardiac resynchronization devices in heart failure patients: results of the ECOST-CRT study. *Europace* 2024;26:3599.
15 Hindricks G, Taborsky M, Glikson M, *et al*. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. *The Lancet* 2014;384:583–90.
16 Varma N, Love CJ, Michalski J, *et al*. Alert-Based ICD Follow-Up. *JACC: Clinical Electrophysiology* 2021;7:976–87.
17 Al-Zaiti SS, Alghwiri AA, Hu X, *et al*. A clinician's guide to understanding and critically appraising machine learning studies: a checklist for Ruling Out Bias Using Standard Tools in Machine Learning (ROBUST-ML). *Eur Heart J Digit Health* 2022;3:125–40.
18 Averbuch T, Sullivan K, Sauer A, *et al*. Applications of artificial intelligence and machine learning in heart failure. *Eur Heart J Digit Health* 2022;3:311–22.
19 Boehmer JP, Hariharan R, Devecchi FG, *et al*. A Multisensor Algorithm Predicts Heart Failure Events in Patients With Implanted Devices. *JACC: Heart Failure* 2017;5:216–25.
20 White-Williams C, Rossi LP, Bittner VA, *et al*. Addressing Social Determinants of Health in the Care of Patients With Heart Failure: A Scientific Statement From the American Heart Association. *Circulation* 2020;141:e841–63.
21 Metra M, Tomasoni D, Adamo M, *et al*. Worsening of chronic heart failure: definition, epidemiology, management and prevention. A clinical consensus statement by the Heart Failure Association of the European Society of Cardiology. *European J of Heart Fail* 2023;25:776–91.
22 Malik A, Gill GS, Lodhi FK, *et al*. Prior Heart Failure Hospitalization and Outcomes in Patients with Heart Failure with Preserved and Reduced Ejection Fraction. *Am J Med* 2020;133:84–94.
23 Butler J, Yang M, Manzi MA, *et al*. Clinical Course of Patients With Worsening Heart Failure With Reduced Ejection Fraction. *J Am Coll Cardiol* 2019;73:935–44.
24 Zanotto G, Capucci A. HeartInsight: from SELENE HF to implementation in clinical practice. *Eur Heart J Suppl* 2023;25:C337–43.