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CLINICAL RESEARCH
Pacing and resynchronization therapy

Risk stratification of cardiovascular and heart failure hospitalizations using integrated device diagnostics in patients with a cardiac resynchronization therapy defibrillator

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Aims Cardiac resynchronization therapy defibrillators (CRT-D) are able to monitor various parameters that may be combined by an automatic algorithm to provide a heart failure risk status (HFRS). We sought to validate the HFRS for stratifying patient risk, evaluate its association with heart failure (HF) symptoms, and investigate its utility for triage of automatic alerts.

Methods and results Data from 722 patients included in the MORE-CARE trial were analysed in a *post hoc* analysis. A high HFRS was associated with a significantly increased risk of admission over the next 30 days with a relative risk for cardiovascular hospitalization (CVH) of 4.5 (95% CI: 3.1–6.6, $P < 0.001$), of HF hospitalization of 6.3 (95% CI: 3.9–10.2, $P < 0.001$) and of non-HF related CVH of 3.5 (95% CI: 2.0–6.9, $P < 0.001$). The negative predictive value of low or medium HFRS for these admissions was ≥98%. A high HFRS was associated with an increased risk of HF symptoms. Of all the automatic remote monitoring alerts generated during the study, only 10% had a high HFRS.

Conclusion The HFRS is able to risk-stratify CRT-D patients, which is potentially useful for managing automatic remote monitoring alerts, by focusing attention on the minority of high-risk patients.

Clinical Trial Registration The trial was registered at www.clinicaltrials.gov under number NCT00885677.

Keywords Cardiac resynchronization therapy • Heart failure • Hospitalization • Symptoms • Risk stratification • Integrated diagnostics • Remote monitoring • Telemedicine

Introduction

Patients implanted with a cardiac resynchronization therapy defibrillator (CRT-D) are at risk for being admitted for cardiovascular (CV) and heart failure (HF) events due to their underlying cardiac dysfunction. These devices are currently able to monitor a number of parameters such as heart rate and rhythm, daily activity, and transthoracic impedance for estimating fluid status (Optivol®). Remote monitoring

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What's new?

- A high heart failure risk status calculated using integrated device diagnostics was associated not only with an increased risk of heart failure hospitalizations, but also of all-cause cardiovascular and non-heart failure admissions.
- The negative predictive value of a low or medium-risk score for these admissions was ≥98%.
- Only 10% of the remote monitoring (RM) alerts had a high risk status.
- This algorithm will be useful to help triage RM alerts.

(RM) alerts generated automatically by threshold crossings place a burden on clinical workload and the data generated by these parameters may be difficult to interpret for many clinicians. These parameters may be combined to yield scores for risk-stratifying patients, thereby facilitating clinical management.[1,2] Cowie *et al.*[3] developed and validated an algorithm to identify patients at risk for HF hospitalization (HFH) in the next 30 days in an ambulatory setting. The algorithm was further validated for HFH on a large cohort of patients from the RAFT trial implanted with an ICD or CRT-D device.[4] Whether the algorithm also predicts all-cause cardiovascular hospitalizations (CVH) and non-HF related CVH is however not known. Finally, risk stratification may assist in triage of automatic RM alerts by limiting phone contacts to patients at highest risk for admission or most likely to be symptomatic.

The MORE-CARE study was an international, prospective, randomized controlled trial conducted in Europe and designed to compare HF management guided by RM vs. standard clinical practice in 865 CRT-D patients.[5] After a median follow-up of 2 years, there were no differences in the primary outcome of mortality and cardiovascular or device-related hospitalizations, with nevertheless a positive impact on the use of healthcare resources. All parameters used in the algorithm (including Optivol®) were available as per protocol. The aims of the present *post hoc* analysis were to evaluate whether the algorithm can be used (i) to stratify risk of CVH (including separate analyses for HFH and non-HF related CVH), (ii) to predict presence of HF symptoms, and (iii) to help with triage of RM alerts.

Methods

Study design and patient population

The details and the main results of the MORE-CARE study have already been published.[5–7] In brief, the MORE-CARE trial randomized 918 patients receiving a CRT-D device to wireless RM (remote group) or to standard care (control group). Patients in the remote group had in-office visits alternating with remote follow-ups with activation of automatic alerts e.g. for atrial fibrillation (AF) and OptiVol® threshold crossings, whereas control group patients had in-office visits only (device diagnostics, including OptiVol®, were nevertheless available for review). Heart failure symptoms were captured by the investigators during in-office visits and also by phone contact in case of alerts in the remote group. An endpoint adjudication committee and an adverse events advisory committee classified all events that potentially contributed to an endpoint or adverse event.

Heart failure risk status

The algorithm considers the following five diagnostic parameters as described in previous studies[3,4]: (i) OptiVol® fluid index (level 1: <30 Ohm-days; level 2: 30–<60 Ohm-days; level 3: 60 to <100 Ohm-days; level 4: ≥100 Ohm-days; level -1: data not available), (ii) night heart rate (NHR) calculated as the average heart rate between mid-night and 4 AM (level 1: 55–85 beats/min; level 2: ≥85 beats/min, ≤55 beats/min, or increasing; level -1: data not available), (iii) duration of activity over a 24-h period, detected by the device piezo-electric sensor (level 1: >60 min/day; level 2: ≤60 min/day or decreasing activity; level -1: data not available), and (iv) heart rate variability measured by the standard deviation of intervals during sinus rhythm (level 1: >60 ms; level 2: ≤60 ms or decreasing; level -1: data not available) (v) a combined heart rhythm parameter including four factors measured over 24 h: (a) AF burden ≥1 h/day, (b) mean ventricular rate during AF ≥90 beats/min AND AF burden ≥1 h/day, (c) one or more shocks for ventricular tachyarrhythmia OR ≥ 5 VT episodes, and (d) CRT pacing ≤ 90% (level 1: only 1 of 4 criteria met; level 2: 2 or more criteria met, level -1: none of the criteria met OR Data not available).The five parameters are computed on a daily basis and a Bayesian belief network approach is used to generate a numeric score and finally a heart failure risk status (HFRS), as shown in *Figure 1*. The algorithm is based on work by Cowie *et al.*[3] who used the device diagnostic parameters and HFH events in their development dataset, then created likelihood tables which associated a specific parameter to probability of HFH. The likelihood tables for all parameters and prior probability of HFH were then combined using Bayesian belief network to compute a numeric score. Bayes' theorem was essentially used to map combination of various parameters (e.g. OptiVol, activity, nocturnal heart rate etc.) to a unique numeric probability of HFH.

In our study, exposure time was fractioned in monthly evaluations for each patient. For each monthly evaluation, the maximum HFRS was determined from the daily risk score of the previous 30 days. The maximum score was used to categorize the monthly evaluations into low (risk score <0.054), medium (risk score 0.054–0.20), and high (risk score ≥0.20) risk. Monthly evaluations were included in the analysis if there were diagnostic data available during the prior 30 days and if clinical follow-up was available during at least 30 days after the evaluation.

The study was approved by the institutional ethics committees, and all patients gave written informed consent to participate.

Statistical methods

The relative risk (RR) of CVH, HFH, non-HF related CVH, and HF symptoms were calculated for medium-risk and high-risk months using low-risk months as a reference and by means of a logistic Generalized Estimating Equation (GEE) model by taking into account multiple events per patient, and reported together with its 95% confidence interval (95% CI). The RR were adjusted by taking into account the effect of the Study Arm. Time to first hospitalization after monthly diagnostic evaluation was estimated using the Kaplan–Meier method. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were evaluated by means of a logistic GEE model taking into account multiple episodes per patient adjusted for the Study Arm.

An alpha-level of 0.05 was considered for each test. All statistical analyses were performed by using SAS 9.3 version software (SAS Institute Inc., Cary, NC, USA).

Results

Of the patients enrolled in the MORE-CARE trial, 722 had complete data relating to the present analysis and were included in this report.

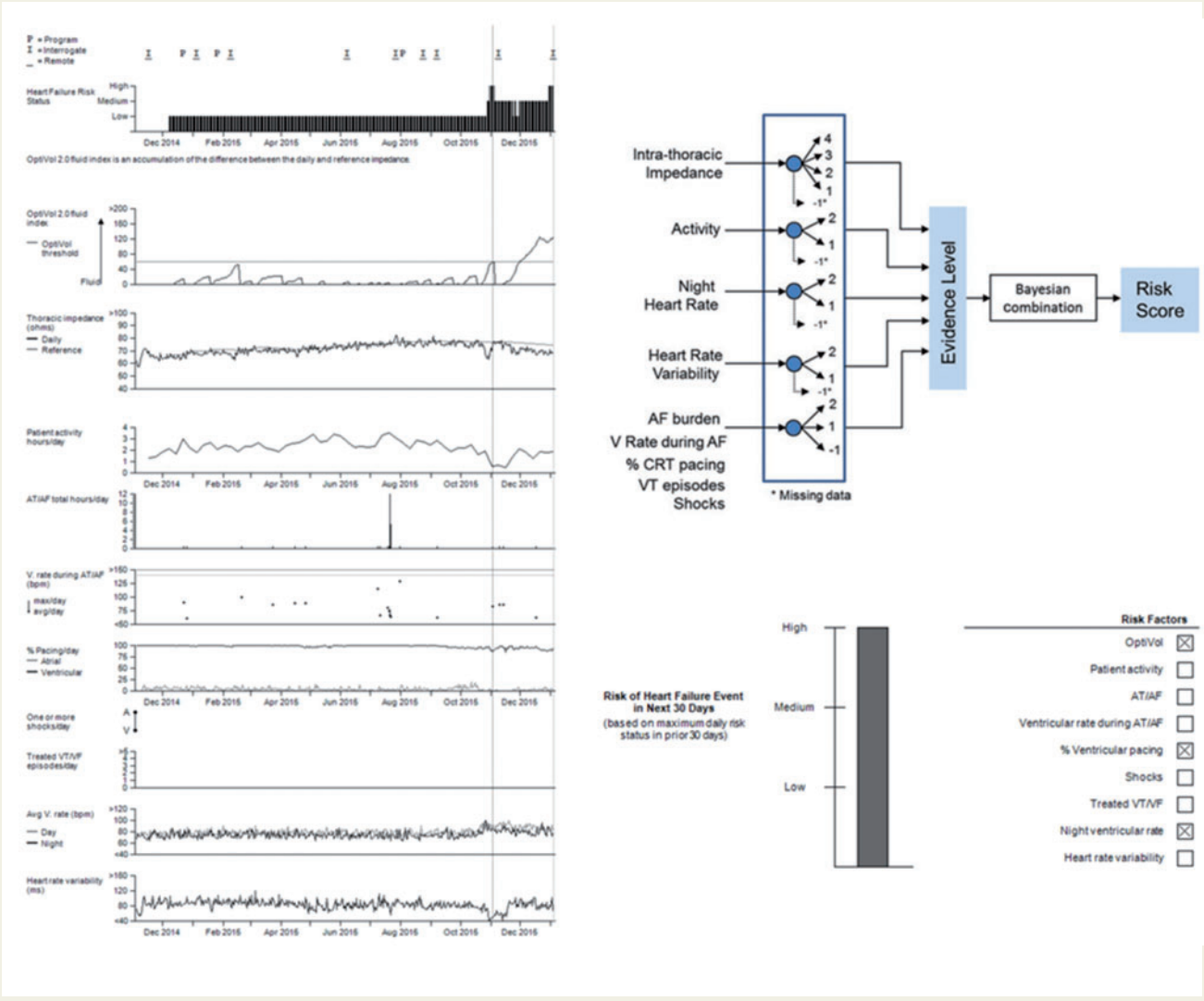


Figure 1 Function of the integrated diagnostics algorithm for generating the heart failure risk status (HFRS). The evolution of the HFRS over follow-up can be seen on the top of the left panel.

Baseline characteristics for included patients are shown in *Table 1*. The patients were followed for a total of 12 430 months (median 20 months per patient, interquartile range 11–23 months). High-risk months represented 10% of the follow-up duration, while the medium-risk and low-risks months comprised 47 and 43%, respectively (*Table 2*).

Cardiovascular hospitalizations

During follow-up, 191 patients experienced a total of 288 CVH, occurring in 268 different months (rate of 2.2% per patient-month). The CVH included HF (49.3%), AF (14.2%), acute coronary syndrome (12.5%), renal insufficiency (6.2%), ventricular arrhythmias (5.2%), bleeding (3.5%), stroke/transient ischaemic attack (3.1%), and other causes (6.0%). Risk of CVH stratified by HFRS is shown in *Table 2*. Kaplan–Meier curves representing cumulative risk of CVH according to risk groups are shown in *Figure 2A*. Data comparing high-risk months with medium and low-risk months combined are shown in *Figure 3A*. This figure also shows that results were consistent in all the subgroup analyses. The sensitivity, specificity, PPV, and NPV of a high-risk score for predicting CVH are shown in *Table 3*.

The association of each of the five risk factors with CVH were significant using univariate analysis, but only Optivol® and activity remained significant upon multivariate analysis (see Supplementary material online, *Appendix*).

Heart failure hospitalization

During the study period, 89 patients experienced a total of 142 HFH in 135 different months (rate of 1.1% per patient-month). Risk of HFH stratified by HFRS is shown in *Table 2*. Kaplan–Meier curves representing cumulative risk of HFH according to risk groups are shown in *Figure 2B*. Data comparing high-risk months with medium and low risk months combined are shown in *Figure 3B*; this figure also shows that results were consistent in all the subgroup analyses.

Table 1 Baseline characteristics of the study population

	n = 722
Age (years), mean ± SD	66 ± 10
Male gender, *n* (%)	549 (76.3)
Ischemic heart disease, *n* (%)	316 (44.1)
History of AF, *n* (%)	125 (17.5)
History of sustained VT/VF, *n* (%)	81 (11.3)
Previous valve surgery, *n* (%)	62 (8.7)
Diabetes, *n* (%)	246 (35.0)
Hypertension, *n* (%)	327 (46.0)
Previous TIA or stroke, *n* (%)	52 (7.3)
COPD, *n* (%)	104 (4.6)
NYHA class at enrollment, *n* (%)	
I	52 (7.3%)
II	226 (31.8%)
III	413 (58.2%)
IV	19 (2.7%)
Not reported	12 (1.7%)
QRS (ms), mean ± SD	155 ± 28
Left bundle branch block, *n* (%)	524 (74.3)
LVEF (%), mean ± SD	27 ± 6
Diuretic, *n* (%)	648 (91.3)
Beta-blocker, *n* (%)	640 (90.1)
ACE-inhibitor or ARBII, *n* (%)	579 (81.5)
Anti-arrhythmic, *n* (%)	183 (25.8)
Anti-platelet, *n* (%)	439 (61.8)
OAC, *n* (%)	160 (22.5)

AF, atrial fibrillation; VT, ventricular tachycardia; VF, ventricular fibrillation; COPD, chronic-obstructive pulmonary disease; NYHA, New York Heart Association; HF, heart failure; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ARBII, angiotensin II receptor blockers; OAC, oral anticoagulants.

The sensitivity, specificity, PPV, and NPV of a high HFRS for predicting 30-day HFH are shown in *Table 3*.

The OptiVol® fluid index used alone for stratifying risk of HFH using <30 Ohm-days as the reference yielded the following results: the RR of 30 to <60 Ohm-days was 2.3 (95% CI 1.5–3.6); of 60 to <100 Ohm-days 1.9 (95% CI 1.0–3.5); and of ≥100 Ohm-days 4.7 (95% CI 2.8–7.9).

The association of each of the five risk factors with HFH was significant when analysed in a univariate approach. Heart rate variability and the combined heart rhythm parameter were no longer significant in the multivariate analysis (see Supplementary material online, *Appendix*).

Non-heart failure related cardiovascular hospitalizations

In order to discount the effect of HFH on total CVH, we performed a separate analysis on 146 CVH that were not due to HF and which occurred in 137 different months (rate of 1.1% per patient-month). The results remained statistically significant (see *Table 2*). Kaplan–Meier curves representing cumulative risk of HFH according to risk groups are shown in *Figure 2C*. Data comparing high-risk months with medium and low-risk months combined are shown in *Figure 3C*. This figure also shows that there were no significant differences between subgroups, although HFRS performed less well in women. The sensitivity, specificity, PPV, and NPV of a high HFRS for predicting 30-day HFH are shown in *Table 3*.

Association of symptoms with risk score

The association of the HFRS and HF complaints and signs is shown in *Table 4*. High-risk months were more often followed by all HF signs and symptoms with respect to low-risk months, except for weight gain. Excluding dyspnea on exertion, similar results were found when medium-risk months were compared with low-risk months.

Table 2 Risk stratification by the HFRS algorithm for cardiovascular, heart failure, and non-heart failure related cardiovascular hospitalizations in the 30 days following low-, medium-, and high-risk months

Evaluation groups according to HFRS score	Months evaluated (%)	Patients (*n*)	Months with hospitalizations (%)	Relative risk (95% CI)	*P*-value
Cardiovascular hospitalization					
Low risk	5300 (43)	653	61 (1.2)	Reference	
Medium risk	5889 (47)	682	132 (2.2)	1.8 (1.3–2.5)	<0.001
High risk	1241 (10)	368	75 (6.0)	4.5 (3.1–6.6)	<0.001
Heart failure hospitalization					
Low risk	5300 (43)	653	30 (0.6)	Reference	
Medium risk	5889 (47)	682	55 (0.9)	1.5 (1.0–2.5)	0.065
High risk	1241 (10)	368	50 (4.0)	6.3 (3.9–10.2)	<0.001
Non-heart failure cardiovascular hospitalization					
Low risk	5300 (43)	653	31 (0.6)	Reference	
Medium risk	5889 (47)	682	79 (1.3)	2.3 (1.5–3.5)	<0.001
High risk	1241 (10)	368	27 (2.2)	3.5 (2.0–6.0)	<0.001

HFRS, heart failure risk status.

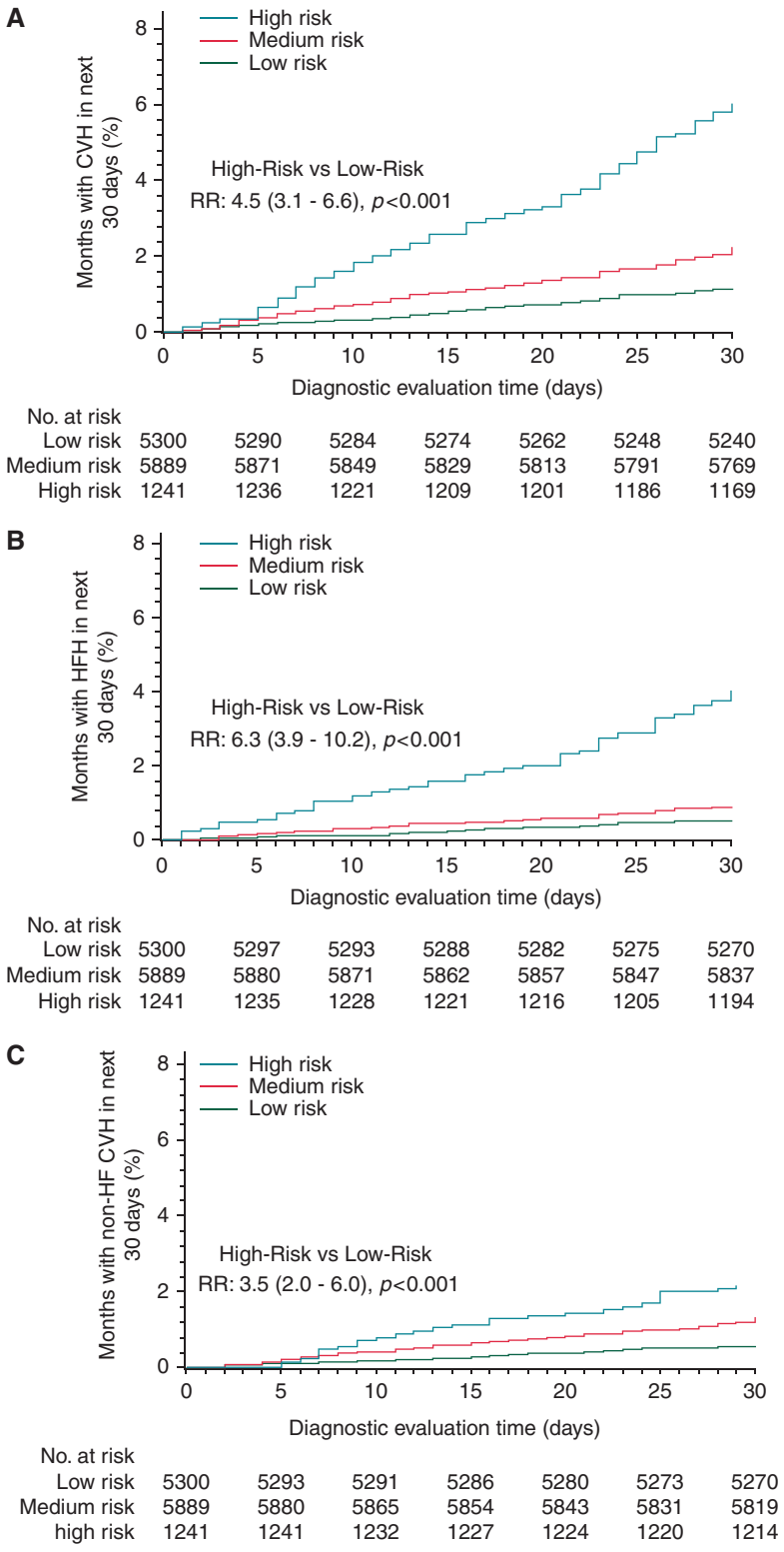
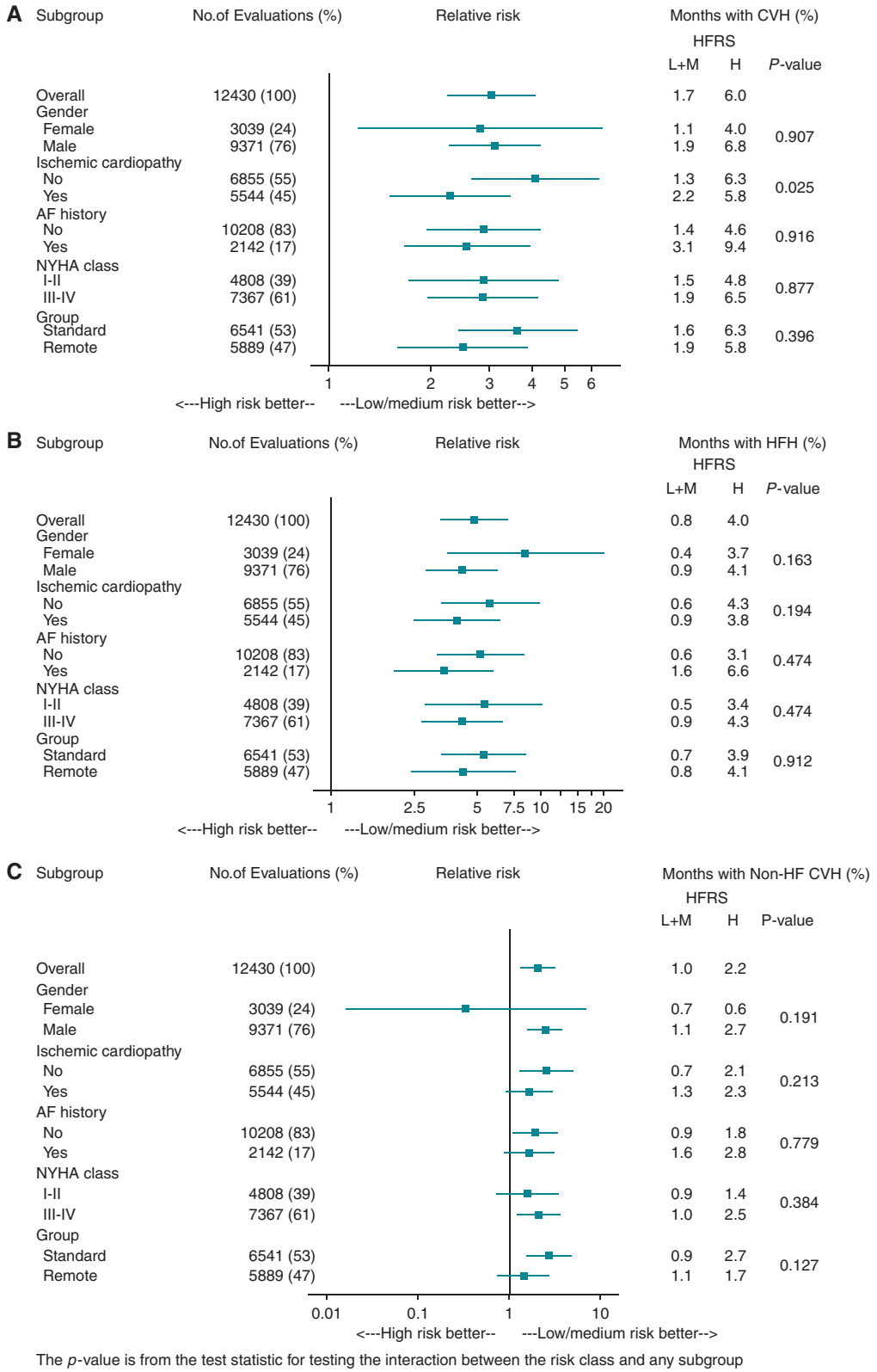


Figure 2 Kaplan–Meier curves of cumulative risk of hospitalization according to integrated diagnostics risk group. (*A*) Heart failure hospitalization, (*B*) cardiovascular hospitalization (including heart failure hospitalization), and (*C*) non-heart failure related CVH.



The *p*-value is from the test statistic for testing the interaction between the risk class and any subgroup variable; x-axis is reported in log scale.

Figure 3 Subgroup analyses of performance of the heart failure risk status (HFRS) evaluating the relative risks of a high HFRS (H) vs. low and medium HFRS combined (L + M) for (*A*) cardiovascular hospitalization (CVH), (*B*) heart failure hospitalization HFH, and (*C*) non-heart failure related CVH.

Table 3 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for a high heart failure risk status (HFRS) for predicting cardiovascular hospitalization, heart failure hospitalization and cardiovascular hospitalization not related to heart failure

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cardiovascular hospitalization	25.5 (18.8–33.6)	90.2 (88.6–91.5)	5.8 (3.9–8.5)	98.0 (97.5–98.4)
Heart failure hospitalization	37.4 (26.5–49.8)	90.1 (88.6–91.5)	4.1 (2.5–6.7)	99.1 (98.7–99.4)
Non-heart failure related cardiovascular hospitalization	15.4 (9.2–24.7)	89.9 (88.3–91.3)	1.7 (0.9–3.0)	98.9 (98.5–99.2)

Values in brackets represent the 95% confidence intervals.
PPV, positive predictive value; NPV, negative predictive value.

Table 4 Association of signs and symptoms of heart failure with heart failure risk status (HFRS)

Sign and symptom	Overall months with sign/ symptom % (*n*/total)	Proportion with low HFRS % (*n*/total)	Proportion with medium HFRS % (*n*/total)	Relative risk* medium HFRS (95% CI)	*P*-value medium HFRS*	Proportion with High HFRS % (*n*/total)	Relative risk* high HFRS (95% CI)	*P*-value high HFRS*
Weight gain	17.9 (503/2804)	18.1 (177/979)	17.3 (247/1430)	1.0 (0.8–1.3)	0.96	20.0 (79/395)	1.2 (0.9–1.7)	0.25
Dyspnea on exertion	53.0 (1516/2861)	47.8 (473/990)	52.8 (770/1459)	1.1 (0.9–1.2)	0.47	66.3 (273/412)	1.6 (1.2–2.0)	<0.001
Orthopnea/PND	11.2 (320/2850)	9.0 (89/990)	10.7 (155/1450)	1.4 (1.1–1.8)	0.020	18.5 (76/410)	2.3 (1.6–3.4)	<0.001
Fatigue/activity reduction	41.4 (1179/2845)	34.9 (346/990)	40.1 (580/1446)	1.2 (1.0–1.5)	0.013	61.9 (253/409)	2.4 (1.8–3.1)	<0.001
Peripheral oedema	10.6 (303/2855)	6.5 (65/995)	10.4 (151/1451)	1.7 (1.3–2.4)	0.001	21.3 (87/409)	3.9 (2.7–5.7)	<0.001

HFRS, heart failure risk status; PND, paroxysmal nocturnal dyspnea.
*Compared to low HFRS and adjusted for remote/in office evaluation.

Remote monitoring alerts

There were a total of 895 automatic alerts generated in the RM group, of which 87 (10%) were classified as high risk, 694 (78%) as medium risk, and 114 (13%) as low risk. Optivol® threshold crossings were present in 569 (64%) of all alerts; 8% were classified as high risk, 92% as medium risk (none were low risk as a threshold crossing of >60 Ohm-days automatically results in a HFRS which is at least medium risk).

Discussion

Our main findings are that a high HFRS (i) allows to stratify risk, not only of HFH (as previously described), but also of CVH and non-HF related CVH, (ii) is associated with presence of HF symptoms and signs, and (iii) is present only in a minority of automatic RM alerts, thereby offering the opportunity to facilitate data triage.

The risk of HFH at 30 days following high risk months was slightly lower in our cohort [relative risk (RR) of 6.3 with 4% incidence] compared with that described by Cowie *et al.*[3] in their validation cohort, pooling predominantly CRT-D patients from different American and European studies (RR of 10.0 with 6.8% incidence). The RR in MORE-CARE was however almost identical compared with the development cohort of their study (RR 6.2). The proportions of high, medium, and low risk months measured automatically by the devices were also very similar (10, 47, and 43% in our study compared with 10, 44, and 45%, respectively in the study by Cowie *et al.*). In a *post hoc* analysis of the RAFT trial conducted in Canada in CRT-D and ICD patients predominantly in NYHA II HF, Gula *et al.* reported a RR of 10.7 of the high-risk months compared with the low-risk months. However the incidence of HFH was lower (2.6%) despite similar proportions of high, medium, and low-risk months (10, 49, and 41%, respectively). This can be explained by differences in the study populations. The RAFT trial included less sick patients who were predominantly in NYHA class II, whereas MORE CARE included NYHA III/IV patients. The absolute risk of HFH for low-risk months was therefore less in RAFT; this resulted in a higher RR of high-risk months when the former were used as a reference.

It should be stated that the PPV of a high-risk month for admission (CVH, HFH, or non-HF related CVH) over the next 30 days was <6%, and that the majority (approximately 60–80%) of these admissions occurred during low/medium risk months. The NPV of a low/medium risk month was however very high (≥98%), which allows the HFRS to be used in clinical practice for data triage, and to focus attention on the 10% of high-risk alerts.

We report for the first time a significant increase in risk of CVH and non-HF related CVH associated with a high HFRS, although the RR were lower than for HFH. This may be explained by the fact that HF and CVH may be affected by common parameters (e.g. cardiac decompensation following an acute coronary event or AF) or may induce similar pathophysiological responses (i.e. adrenergic activation). Furthermore, the algorithm captures different events which may be associated with CVH (e.g. AF).

In agreement with data from Gula *et al.*[4] we found that a high HFRS score is associated with worsening symptoms. This is valuable from a clinical standpoint, as presence of symptoms increases the likelihood of actionable events with remote device management.

In a recent survey by the European Heart Rhythm Association, over a quarter of the centres cited increased workload as being a barrier to implementation of RM of CRT devices.[8] Triage of the automatic alerts using the HFRS score will no doubt be a useful to help workflow, for instance by only considering alerts with a high HFRS score and those with AF. The REM-HF study has been recently been published,[9] and showed no advantage of weekly scheduled transmissions compared with usual care in terms of mortality or unplanned CVH. One of the reasons for the negative results may have been data overload, hampering interpretation and thus limiting meaningful actions.

The question remains whether RM using HFRS has any impact on patient outcome. A meta-analysis of nine randomized controlled trials involving 6469 patients did not show any significant effect of RM of ICD and CRT-D patients on mortality or hospitalization, but these trials did not involve alerts for fluid status.[10] Similar results were reported by a more recent meta-analysis including 11 trials focused on RM in systolic HF.[11] In an analysis of 21 217 patients on the Medtronic CareLink® Discovery Link, Tang *et al.*[12] reported that patients who had Optivol® threshold crossings within the first 6 months had a two-fold increase in mortality. However, patients who did not have any further crossings had better outcome compared with those who did (HR 0.48, $P < 0.001$). This raises the question of whether timely treatment of high-risk patients identified by fluid threshold alerts may avert clinical deterioration. Recently, the OptiLink-HF trial[13] randomized 1002 patients (62.6% of whom had a CRT-D) to RM (which included Optivol® alerts) vs. standard care, and did not find any differences in mortality or hospitalization. Our MORE CARE trial also included the same alerts and did not show any improvement in clinical outcome with RM.[7] However, the HFRS was not available for use in these studies and hence was not used to guide therapy, and the question still requires further study.

Study limitations

This is a *post hoc* analysis, which nevertheless evaluated pre-defined endpoints. The results refer to devices with the proprietary Medtronic Optivol® algorithm, and may not apply to similar scores derived from other manufacturers. It has been shown that the number and duration of Optivol® threshold crossings and low average impedance have prognostic implications.[2,12,14,15] The HRFS does not take this information into account, and may perform even better using these data.

Conclusions

Risk-stratification using strategies that integrate data derived by implantable devices is likely to play an increasing role in patient management. Our study contributes to validating the HFRS for predicting HFH, and shows for the first time that CVH is also predicted by this risk stratification scheme. Integrated diagnostics are likely to be of great help to triage alerts generated by RM (and also scheduled transmissions) by focusing on the minority of events that are at highest risk. A next step will be to determine whether the HFRS may improve patient outcome by treating high-risk patients before clinical deterioration.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: H.B. has received speaker fees and institutional fellowship support from Biotronik, Boston Scientific, Liva Nova, Medtronic, and St Jude Medical. G.B. has received minor speaker's fees from Medtronic and Boston Scientific. N.C. received consulting fees from Medtronic. A.D.C. has received research grants and honoraria for consultancy and speaker fees from Medtronic, Boston Scientific, and Saint Jude medical. S.F. has received minor speaker fees from Bayer. R.P.R. has received minor consulting fees from Medtronic. G.B. has received minor speaker's fees from Medtronic and Boston Scientific. L.M. and V.S. are employees of Medtronic. A.Q. and S.F.V. have no conflict of interest to report.

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