

# Potential value of automated daily screening of cardiac resynchronization therapy defibrillator diagnostics for prediction of major cardiovascular events: results from Home-CARE (Home Monitoring in Cardiac Resynchronization Therapy) study

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**Aim** To investigate whether diagnostic data from implanted cardiac resynchronization therapy defibrillators (CRT-Ds) retrieved automatically at 24 h intervals via a Home Monitoring function can enable dynamic prediction of cardiovascular hospitalization and death.

**Methods and results** Three hundred and seventy-seven heart failure patients received CRT-Ds with Home Monitoring option. Data on all deaths and hospitalizations due to cardiovascular reasons and Home Monitoring data were collected prospectively during 1-year follow-up to develop a predictive algorithm with a predefined specificity of 99.5%. Seven parameters were included in the algorithm: mean heart rate over 24 h, heart rate at rest, patient activity, frequency of ventricular extrasystoles, atrial–atrial intervals (heart rate variability), right ventricular pacing impedance, and painless shock impedance. The algorithm was developed using a 25-day monitoring window ending 3 days before hospitalization or death. While the retrospective sensitivities of the individual parameters ranged from 23.6 to 50.0%, the combination of all parameters was 65.4% sensitive in detecting cardiovascular hospitalizations and deaths with 99.5% specificity (corresponding to 1.83 false-positive detections per patient-year of follow-up). The estimated relative risk of an event was 7.15-fold higher after a positive predictor finding than after a negative predictor finding.

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<b>Conclusion</b>	We developed an automated algorithm for dynamic prediction of cardiovascular events in patients treated with CRT-D devices capable of daily transmission of their diagnostic data via Home Monitoring. This tool may increase patients' quality of life and reduce morbidity, mortality, and health economic burden, it now warrants prospective studies.
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<b>Keywords</b>	Remote device monitoring • Cardiac resynchronization therapy defibrillator • Multiparameter predictor • Cardiovascular hospitalizations • Heart failure • Home monitoring

## Introduction

Permanent implantation of a cardiac resynchronization device combined with defibrillator function (CRT-D, cardiac resynchronization therapy defibrillator) is recommended to reduce morbidity and mortality in patients in New York Heart Association (NYHA) class III–IV who are symptomatic despite optimal medical therapy, and who have a reduced left ventricular ejection fraction ( $\leq 35\%$ ) and QRS prolongation ( $\geq 120$  ms).<sup>1</sup> Most CRT-D recipients are elderly and have comorbidities, such as coronary heart disease, atrial fibrillation, primary hypertension, lung disease, diabetes, renal dysfunction, or anaemia, that bring additional risk of hospitalization and death.<sup>2–4</sup> To improve clinical outcomes and reduce health economic burden, CRT-Ds will probably evolve and embrace additional features necessary to dynamically stratify the risk not only for acute decompensated heart failure (ADHF),<sup>5–7</sup> but also for other major cardiovascular events.

Nowadays, CRT-D devices are capable of measuring a variety of parameters beyond heart rhythm and of transmitting measured values remotely to the physician.<sup>6–11</sup> The following parameters may warn of impending ADHF or other cardiovascular events and predict poor clinical outcome: (i) sustained decrease in thoracic impedance due to lung fluid retention<sup>5–8,12–15</sup> (measured between a lead in the right ventricle and the generator in the left pectoral region or using alternative current pathways);<sup>16–18</sup> (ii) low heart rate variability, indicating sympathetic dominance in cardiac autonomic control;<sup>6,7,12,19–22</sup> (iii) a high resting heart rate or relatively high mean heart rate over 24 h;<sup>6,19,21,23–25</sup> (iv) decreased patient activity, potentially reflecting exercise intolerance;<sup>7,12,19–21</sup> (v) increased frequency of ventricular extrasystoles;<sup>26</sup> (vi) ventricular tachyarrhythmia episodes or defibrillation shocks;<sup>7,27,28</sup> (vii) prolonged duration of atrial fibrillation;<sup>7,21,22</sup> (viii) rapid ventricular rate during atrial fibrillation;<sup>7,21</sup> (ix) reduced cardiac resynchronization pacing percentage, indicating a failure in the electrical treatment of cardiac asynchrony;<sup>7,29</sup> (x) minute ventilation disturbances;<sup>30</sup> and (xi) haemodynamic deterioration monitored with impedance-based or pressure sensors.<sup>8,16,18,31,32</sup> Combining several of these parameters into a single algorithm may improve the overall ability to risk-stratify patients with implanted devices.<sup>7,33</sup>

Current dynamic risk stratification algorithms must either be simple enough for implementation into implantable devices with generally modest data processing capacity, or, if data analysis is performed in service centres using more complex predictive algorithms, these must still be based on a sporadic inflow of remotely acquired data from the implanted devices at intervals ranging

from several days to several weeks. These restrictions limit application of present algorithms to ADHF with a positive predictive value of 3.85% (1 correct out of 27 alarms, resulting in 2.7 false positive (FP) alarms per patient-year) and a sensitivity of  $< 65\%$  in larger patient cohorts.<sup>7</sup>

However, the advent of remote monitoring systems capable of automatic daily transmission of device diagnostic data to a service centre<sup>9,10</sup> will possibly pave the way for multifaceted risk stratification algorithms. By detecting pathophysiological changes before their overt effect on the patient's clinical status, the multifaceted algorithms may increase the scope of cardiovascular events that can be risk stratified. In the Home Monitoring in Cardiac Resynchronization Therapy (Home-CARE) study, we investigated whether device diagnostic data retrieved automatically in 24 h intervals via a Home Monitoring function (Biotronik SE & Co. KG, Berlin, Germany) may enable dynamic prediction of major cardiovascular events including, but not limited to, ADHF.

## Methods

Home-CARE was a prospective, non-randomized, multicentre observational study carried out between March 2005 and August 2008 at 48 investigational sites in seven European countries and Israel (Appendix). The aim of the study was to develop an automated algorithm that would use daily Home Monitoring data to predict deaths and hospitalizations (at least one overnight stay) due to cardiovascular reasons. Clinical and Home Monitoring data were prospectively collected during 1-year follow-up.

The predictor was developed based on data recorded by CRT-D models Kronos LV-T and Lumax HF-T (Biotronik SE & Co. KG, Berlin, Germany). The data were transmitted automatically from the implanted devices to the Biotronik Home Monitoring Service Centre each day, in the early morning hours, independent of patient or physician interaction. Since Lumax HF-T offered more parameters of potential predictive value than Kronos LV-T, we tested a so-called add-on strategy for predictor development. A basic predictor was developed first, based on five selected parameters available in both CRT-D models. Then, an enhanced predictor was developed including two additional Lumax HF-T parameters. The aim of the add-on strategy is to improve the yield of risk-stratification algorithms by considering new sensors on top or instead of parameters and sensors available in older-generation devices.

The study was conducted according to the Good Clinical Practice Guidelines and the Declaration of Helsinki. Central Ethics Committee approval was obtained for all German sites according to the rules of all participating centres. Non-German sites had country-specific institutional review board approval processes according to the

corresponding national laws. All patients provided written informed consent.

## Patients

Home-CARE enrolled 515 patients who had an indication for the implantation of a cardiac resynchronization device and who were hospitalized at least once because of heart failure within 12 months before enrolment. Patients were not admitted to the study if they had permanent atrial fibrillation, unstable angina pectoris or a myocardial infarction within the last 3 months, a cardiac intervention planned within the next 3 months (e.g. coronary artery bypass graft, percutaneous transluminal coronary angioplasty, heart transplantation), acute myocarditis, life expectancy <6 months, age <18 years, or if their place of residence during follow-up was likely to change. Further exclusion criteria were: pregnant or breast-feeding women, participation in another clinical study, or living in an area with insufficient mobile phone coverage for Home Monitoring.

The present analysis comprised all enrolled patients treated with CRT-D devices. The 377 patients represent a typical CRT-D cohort with respect to age, gender, and aetiology (Table 1).<sup>7</sup> Furthermore, 55.7% of patients had ischaemic aetiology of heart failure and 83.3% had NYHA class III or IV symptoms. Most patients were receiving diuretics (88.2%; half of them aldosterone antagonists), beta-blockers (77.0%), and angiotensin-converting enzyme inhibitors (78.7%).

## Cardiovascular events and control data sets

A total of 201 cardiovascular hospitalizations and 8 cardiovascular deaths without prior hospitalization were reported during the mean follow-up period of  $335 \pm 135$  days (median 368 days). As delineated in Table 2, the predictor development procedure did not include planned cardiovascular interventions, device-related hospitalizations, events occurring too early after implantation (<30 days, a stabilization period) or too early after previous hospitalization (<30 days, not allowing sufficient monitoring window before readmission), events that were not preceded by regular Home Monitoring data transmission, and insufficiently documented events that could not be positively adjudicated for inclusion in predictor development by the event committee (Appendix).

After eliminating unsuitable events on these grounds, 72 events qualified for predictor development. The most prevalent events were hospitalization for worsening heart failure ( $n = 38$ ; 52.8%), for ventricular or atrial rhythm disturbances ( $n = 15$ ; 20.8%), or for angina pectoris ( $n = 7$ ; 9.7%). Less prevalent events were hospitalizations due to syncope ( $n = 4$ ; 5.6%), peripheral vascular emergency ( $n = 3$ ; 4.2%), stroke ( $n = 2$ ; 2.8%), or transient ischaemic attack ( $n = 1$ ; 1.4%), as well as out-of-hospital cardiovascular deaths ( $n = 2$ ; 2.8%). Twenty-six of the 72 events occurred in the Lumax HF-T subpopulation and were thus eligible for the development of the enhanced predictor with two additional parameters.

Control patients were chosen randomly from enrolled patients who were free of cardiovascular hospitalization or death and who had at least 50 days of Home Monitoring coverage during follow-up, disregarding the first 30 days after implantation. The numbers of control patients were selected to be symmetrical to the number of cardiovascular events, requiring 72 controls for the basic predictor and 26 controls for the enhanced predictor.

As explained later in this section, the specificity of the predictive algorithms was fixed to 99.5% by a computed algorithm optimization procedure. For this reason, inclusion of additional control patients in the algorithm optimization procedure would not have altered

**Table 1** Baseline characteristics of 377 patients included in predictor development

Parameter	n = 377
Age (years), mean (SD)	66.2 (10.0)
Female, %	21.5
LVEF (%), mean (SD)	24.5 (7.5)
% of patients with LVEF $\leq$ 35%	90.7
LVEDD (mm), mean (SD)	67.8 (15.8)
Aetiology of heart failure, %	
Ischaemic (of which, myocardial infarction)	55.7 (75.2)
Non-ischaemic	44.3
NYHA class, %	
I	0.8
II	14.9
III	74.8
IV	8.5
QRS duration (ms), mean (SD)	158 (41)
% of patients with QRS $\geq$ 130 ms, %	81.9
Left/right bundle branch block, %	66.8/6.6
ICD indication, %	
Cardiac arrest with documented VT/VF	8.0
Primary prevention	58.7
Other	32.8
No ICD indication	0.5
Sinus bradycardia (<50 b.p.m), %	5.8
History of atrial fibrillation, %	21.8
History of ventricular arrhythmia, %	42.4
Comorbidities, %	
Hypertension	37.1
Diabetes	30.8
Renal insufficiency	25.7
COPD	11.1
Major symptoms, %	
Dyspnoea	74.8
Dizziness	26.5
Syncope	15.6
Peripheral oedema	27.3
Angina pectoris	24.7
Heart palpitations	17.2
Medication, %	
Diuretic	88.2
Beta-blocker	77.0
ACE inhibitor	78.7
Anticoagulant	67.2
Antiarrhythmic	27.2
Digitalis	26.9
Antianginal	10.6
Ca channel blocker	7.6
Implanted CRT-D device, n (%)	
Kronos LV-T	245 (65.0)
Lumax HF-T	132 (35.0)

ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization device with defibrillator; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; NYHA, New York Heart Association; SD, standard deviation; VF, ventricular fibrillation; VT, ventricular tachycardia.

**Table 2 Events: classification and exclusions before predictor development**

Event	Number of events	Number of patients affected
All-cause hospitalization	306	176
All-cause death	36	36
In-hospital death	13	13
Out-of-hospital death	23	23
Cardiovascular events	209	135
Hospitalization	201	130
Out-of-hospital CV death	8	8
Exclusions before predictor development		
Planned CV interventions <sup>a</sup>	13	12
Device-related CV hospitalization (e.g. lead revision, inadequate shock)	58	49
CV hospitalization without sufficient clinical documentation <sup>b</sup>	25	21
<30 days of HM coverage before CV hospitalization <sup>c</sup>	9	7
CV hospitalization not preceded by regular HM data transmission	26	17
Out-of-hospital CV death preceded by <30 days of HM coverage	2	2
Out-of-hospital CV death not preceded by regular HM data transmission	2	2
Out-of-hospital CV death preceded by no HM data transmission at all	2	2
Cardiovascular events used for predictor development and evaluation	72	57
Hospitalization (basic predictor/enhanced predictor <sup>d</sup> )	70/26	55/20
Death not preceded by CVH (basic predictor/enhanced predictor <sup>d</sup> )	2/0	2/0

CV, cardiovascular; HM, Home Monitoring.

<sup>a</sup>Ablation procedures, bypass surgery, and heart transplantation.

<sup>b</sup>For example, neurologically mediated problems, dyspnea of unknown cause, or other less well-documented events that could not be positively adjudicated for inclusion in predictor development by the event committee.

<sup>c</sup>Events were excluded if occurring either too early after implantation (a stabilization period) or too early after previous hospitalization (not allowing sufficient monitoring window before readmission).

<sup>d</sup>Enhanced predictor was developed on subpopulation with Lumax HF-T devices.

predictor specificity (i.e. the rate of FPs), while, on the other hand, it would have considerably prolonged computational time. Therefore, the use of symmetrical numbers of events and controls appeared to be an optimal solution for this study that was concerned with the feasibility of a cardiovascular risk stratifier rather than with the evaluation of its prospective clinical performance.

## Home monitoring parameters included in predictive algorithms

The basic predictor was composed of:

- (i) mean heart rate during 24 h;
- (ii) heart rate at rest, represented by the lowest 10 min average value among all 10 min average values determined successively within a resting period defined by the user (e.g. from 1 a.m. to 5 p.m.);
- (iii) patient activity, assessed using an in-built accelerometer sensor and expressed in per cent of 24 h, where a minute was considered 'active' if the current sensor rate was greater than or equal to the activity threshold;
- (iv) right ventricular apical pacing lead impedance, calculated from four measurements per day; and
- (v) the number of ventricular extrasystoles during 24 h.

The enhanced predictor also included:

- (vi) heart rate variability, assessed via daily standard deviation of 5-minute average atrial-atrial intervals recorded every 5 min;
- (vii) painless shock impedance, a kind of thoracic impedance,<sup>17</sup> derived from four measurements per day.

These seven parameters were selected because their subtle changes and potential relationships may not be readily recognized in regular Home Monitoring data, in contrast to single events such as ventricular tachyarrhythmia, defibrillation shock, atrial fibrillation, or low percentage of cardiac resynchronization that can all be brought to the physician's attention through immediate notifications, so-called event reports. Furthermore, a mixture of both—trend changes and selected single events—is included in a web-based visualization tool called 'Heart Failure Monitor' that can be used routinely for patient monitoring.

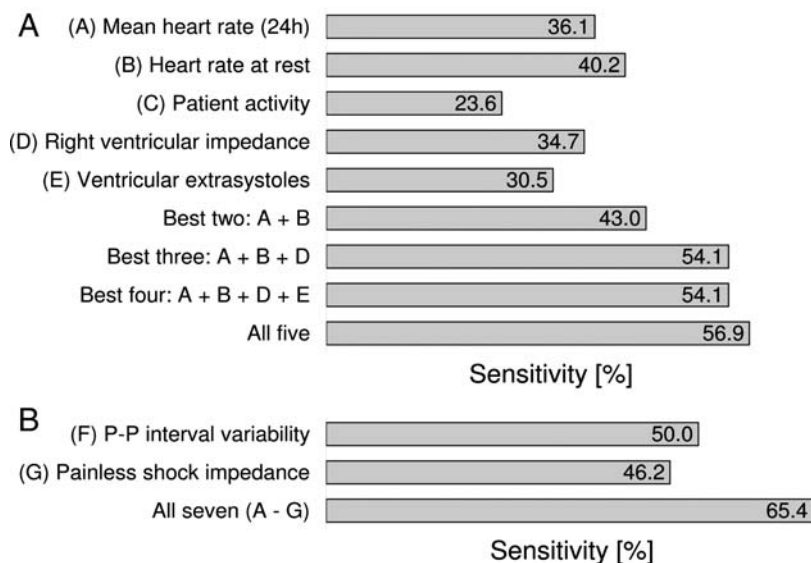
On the other hand, several parameters mentioned in the Introduction section as potentially valuable, including conventional thoracic impedance, minute ventilation, and haemodynamic changes, could not be recorded with the devices used and were not considered.

## Monitoring window for predictor

A 25-day time window ending 3 days before cardiovascular hospitalization or 3 days before cardiovascular death without prior hospitalization was used for predictor development and was referred to as 'the monitoring window'. This was a running window, updated everyday, as opposed to a series of discrete windows (updated e.g. every 30 days) that were suitable for ADHF risk stratification based on data recorded by implanted devices that were not engaged in daily, automated remote data transmission.<sup>7</sup> In our study, the 25-day running window was positioned in a way to enable the predictive algorithm to raise an alert at least 3 days before an upcoming event. Even if the alert was raised at the weekend, the physician would thus have at least 1 day to react and try to avert hospitalization or an impending event by pre-emptive therapy.

## Predictor development and evaluation

Predictive algorithms were developed for each parameter of the basic predictor and then for the best two parameters combined, best three, best four, and all five parameters, using 72 events that qualified for predictor development (Table 2). In the next step, predictive algorithms were developed for two additional parameters in the enhanced predictor and then for all seven parameters, using 26 events that occurred in the Lumax HF-T subpopulation.



**Figure 1** Sensitivity values for the basic five-parameter predictor (A) and for the enhanced seven-parameter predictor (B), to detect major cardiovascular events from Table 3. In (A), combinations of two, three, and four parameters were made by adding the next best individual parameter. (B) shows the sensitivities for two new parameters and for the combination of all seven parameters. The combination of the two new parameters from (B) without 'help' of parameters from (A) had still suboptimal sensitivity of 50% (not shown). All sensitivity values were calculated retrospectively for the target specificity of 99.5%.

Parameters (i.e. their significant counts) were added in a linear combination to generate weighted trends. To achieve the highest sensitivity at the predefined specificity of 99.5%, the weights were trained and optimized using the Powell optimization method.<sup>34</sup> Like other optimization methods, the Powell coordinate ascent method systematically varies the weights of the linear combination. The task of the stepwise procedure is to maximize an objective function—the sensitivity. For this procedure, days in control patients (without cardiovascular events) were classified as true negative (TN) if weighted trend was below the threshold or as FP if weighted trend crossed the threshold. The specificity of a predictive algorithm is 1 minus the rate of FP alarms determined as:  $FP/(TN + FP)$ . Thresholds for weighted trends were adjusted to result in 99.5% specificity (i.e. rate of FP alarms of 0.5%) for any parameter combination, leading in prospect to a maximum of 1.83 FP alarms per patient-year of monitoring (0.5% of 365 days).

Sensitivity values were then calculated retrospectively for the individual parameters and their combinations. A predictive algorithm delivered a true positive (TP) prediction of an event if weighted trend crossed the threshold within the 25-day monitoring window, otherwise the prediction was false negative (FN). The sensitivity was determined as:  $TP/(TP + FN)$ .

For the enhanced predictor composed of all seven parameters, we calculated the positive ( $=TP/[TP + FP]$ ) and the negative predictive values ( $=TN/[TN + FN]$ ). A modified receiver operating characteristic curve was constructed by plotting the sensitivity and FP rate as a function of varying threshold for weighted trends.

We also calculated the relative risk of event occurrence after a positive predictor finding vs. event occurrence after a negative predictor finding. For mathematical formulation, it was assumed that each alert stated lasts for 30 days and that alerts are not overlapping. Since the number of FPs was larger than the number of TPs, and the total alert rate on the data pool was estimated to be 2.51 per patient-year, the relative risk was calculated using the formula:  $relative\ risk = sensitivity \times (12/2.51 - 1)/(1 - sensitivity)$ .

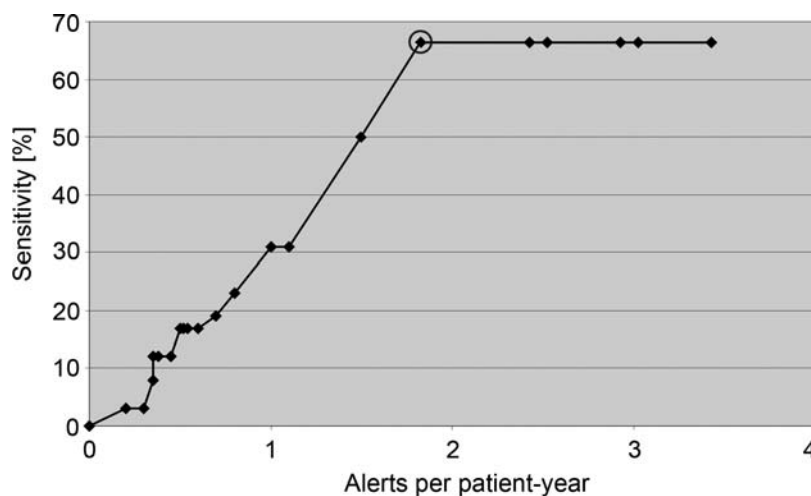
## Results

The projected sensitivity of the individual Home Monitoring parameters to predict major cardiovascular events ranged from 23.6% for patient activity to 50.0% for P–P interval variability (Figure 1A and B). The basic predictor composed of five parameters was associated with a sensitivity of 56.9%. The enhanced predictor with seven parameters reached a sensitivity of 65.4%, indicating the value of the add-on strategy. This sensitivity means that nearly two-thirds of major cardiovascular events (not occurring within 30 days of implantation or within 30 days after previous hospitalization) may be predicted in conjunction with a specificity of 99.5%, equivalent to 1.83 FP alarms per patient-year, used as fixed input for the algorithm optimization procedure.

The modified receiver operating characteristic curve in Figure 2 shows that variation of the threshold for weighted trends may reduce sensitivity for better specificity (less FP alarms per patient-year of monitoring). In our opinion, the optimal point on the curve for the enhanced predictor had a sensitivity of 65.4% and 1.83 false-positive detections per patient-year of monitoring, corresponding to positive and negative predictive values of 7.83 and 99.96%, respectively. By comparison, the basic predictor composed of five parameters had the same negative predictive value and a lower (5.99%) positive predictive value. The estimated increase in the likelihood of an event after a positive predictor finding was 7.15 for the enhanced predictor and 4.99 for the basic predictor.

Figure 3 illustrates how moderate changes in several parameters were combined by the enhanced predictive algorithm into a significant finding in a patient who was hospitalized for heart failure





**Figure 2** Modified receiver operating characteristic curve for the enhanced seven-parameter predictor. Plots show the trade-off between sensitivity to detect impending cardiovascular hospitalization or death and the number of false-positive detections per patient-year of monitoring, as a function of varying thresholds for weighted trends. The optimal point is indicated by the circle.

worsening. As seen, P–P interval variability was decreasing and the number of ventricular extrasystoles, mean heart rate, and heart rate at rest were increasing. While it would be difficult to make a clear cut decision based on any individual trend in this case, the combination of several parameters increased the level of certainty about ongoing pathophysiological changes.

Table 3 shows that both basic and enhanced algorithms could retrospectively best predict the two most prevalent event types, namely hospitalization for heart failure worsening and hospitalization for atrial or ventricular rhythm disturbances. This outcome may be a consequence either of a stronger contribution of prevalent than rare events to algorithm training or of current limitations in sensor/device technology.

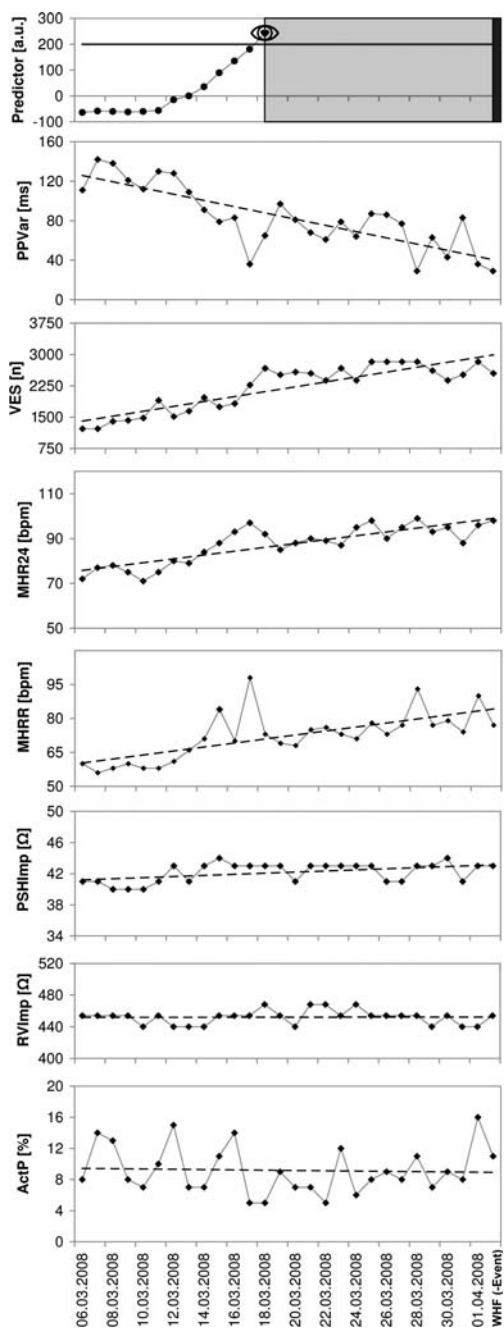
## Discussion

In an effort to take advantage of the automatic, daily diagnostic data transmission capability of the newest CRT-D devices, we developed a first automated algorithm for dynamic prediction of major cardiovascular events including but not limited to ADHF. According to the add-on strategy that strives to improve the predictive power by including new sensors on top or instead of older parameters, the algorithm comprised seven parameters and reached retrospective sensitivity of 65.4%, for a target specificity of 99.5% that corresponds to 1.83 FP alarms per patient-year.

As no other algorithms are available to predict all-cause cardiovascular hospitalizations using remotely transmitted data from implantable devices, no meaningful comparison of our study data with literature can be made. Algorithms somewhat similar to ours are those that stratify the risk of ADHF either based on a single parameter such as thoracic impedance<sup>13</sup> (the oldest concept, now in advanced stage of clinical evaluation, with the composite of all-cause mortality or heart failure hospitalization serving as the primary endpoint)<sup>35</sup> or heart rate variability,<sup>19</sup> or

based on the combination of eight parameters: thoracic impedance, atrial fibrillation duration, ventricular rate during atrial fibrillation, patient activity, night heart rate, heart rate variability, cardiac resynchronization therapy (CRT) pacing percentage, and defibrillation shocks.<sup>7</sup> These ADHF-related algorithms have a prospectively validated sensitivity in the range of 60–70% (either explicitly stated or derivable from provided data), which is similar to our findings, but they have more FP alarms (2.4–2.7 per patient-year of monitoring)<sup>7,13,19</sup> and a lower positive predictive value (3.85 vs. 7.83% in our study).<sup>7</sup> Direct comparison with our study findings is difficult not just because of the different scope of cardiovascular events that were targeted for prediction, but also due to major differences in study methodology in that the ADHF-related studies mostly validated algorithm performance prospectively and did not make use of daily, automated data transmission for remote dynamic risk stratification,<sup>7,13,19</sup> which is associated with a substantially different way of determining specificity, FP alarm rate, and positive or negative predictive values.

A common limitation of all predictive algorithms studied so far is that they may predict some but not all cardiovascular events leading to hospitalization or death. The sensitivity and specificity of ADHF-related algorithms is, for example, determined by taking into account only heart failure events associated with pulmonary congestion, which requires a strict and independent adjudication by an adverse event advisory committee prior to data evaluation.<sup>7</sup> The current algorithm pools all cardiovascular events together, essentially not differentiating between types of events. Nevertheless, planned cardiovascular interventions and device-related hospitalizations, which accounted for 34% of all cardiovascular events, had to be excluded from predictor development and evaluation. Since algorithm-based predictions cannot be made using ‘snapshot’ data (single Home Monitoring data transmissions), but only based on trends in successive data transmissions during 30 days, ~20% of all events had to be excluded due to an insufficient



**Figure 3** Example of parameter trends and the resulting combined predictor line (upper panel) in a patient hospitalized for heart failure worsening on 5 April 2008. The seven-parameter predictor reached threshold (beginning of the grey area) 16 days before hospitalization. The threshold was set at 200 arbitrary units as a result of the algorithm optimization process described in the section Methods, and corresponds to a hazard ratio of 7.15. ActP, patient activity; a.u., arbitrary units; bpm, beats per minute; MHR24, mean heart rate during 24 h; MHRR, heart rate at rest; PPVar P–P interval variability; PSHImp, painless shock impedance; RVImp, right ventricular impedance; VES, ventricular extrasystoles; WHF, worsening heart failure.

**Table 3** Cardiovascular events used for predictor evaluation

Event	Correctly 'predicted' events/events used for predictor evaluation	
	Basic predictor <sup>a</sup>	Enhanced predictor <sup>b</sup>
Total events	41/72	17/26
Hospitalization		
Worsening heart failure	25/38	9/15
Rhythm disturbance	10/15	4/6
Angina pectoris	1/7	1/1
Syncope	1/4	1/1
Peripheral vascular emergency	1/3	0/1
Stroke	1/2	1/1
Transient ischaemic attack	0/1	1/1
Death <sup>c</sup>	2/2	0/0

<sup>a</sup>Developed on data from 377 patients with Kronos LV-T and Lumax HF-T devices, using five Home Monitoring parameters ('all five' in Figure 1A).

<sup>b</sup>Developed on data from 132 patients with Lumax HF-T devices, using seven Home Monitoring parameters ('all seven' in Figure 1B).

<sup>c</sup>Caused by stroke (n = 1) and recurrent ventricular fibrillation secondary to worsening heart failure (n = 1).

amount of Home Monitoring data received before the event. Finally, 12% of events were not sufficiently documented to be sure of their cardiovascular nature, which altogether reduced the total number of events eligible for predictor development and evaluation to about 34% of all suspected cardiovascular events during the present study.

The monitoring window for the predictor was positioned to allow a reasonable 3-day 'intervention window' for the physician to react with pre-emptive treatment following an alert in the future. Extension of the monitoring window closer to impending events (i.e. shortening of the intervention window) has the potential to improve the predictive yield, since changes in parameters are generally intensified soon before an event. Shorter intervention windows may become feasible in the future, when remote alert systems receive broader acceptance and clinics develop processes and adjust workflows for a quicker response to alerts resulting in earlier patient intervention. However, predicting an event does not necessarily mean that it can be minimized by appropriately targeted treatments. This has to be demonstrated in a comparative prospective study.

### Increasing use of cardiac resynchronization therapy defibrillators in heart failure patients

The implantation rate of cardiac resynchronization devices in Western Europe increased from 46 per million inhabitants in 2004–100 per million in 2008, of whom 75% of patients received CRT-D devices and 25% received CRT alone.<sup>36,37</sup> A large survey of

current practice associated with CRT(-D) implantations recruited 2438 patients from 141 centres in 13 Western European countries, and provided important information with regard to patient demographics, selection criteria, procedural routines, and status at discharge.<sup>36</sup> Recently, indications for CRT(-D) therapy with level of recommendation I and level of evidence A have been expanded to include patients with less symptomatic heart failure (NYHA class II, ejection fraction  $\leq 35\%$ , QRS  $\geq 150$  ms), to reduce morbidity or prevent disease progression.<sup>1</sup> This will expand the CRT(-D) patient population that may benefit from future risk-stratification algorithms utilizing diagnostic data retrieved from implanted devices.

## Outlook

According to the add-on strategy, the enhanced predictive algorithm developed in this study could possibly be strengthened further by inclusion of thoracic impedance measurements, especially in the risk stratification for ADHF.<sup>5–8,12–15</sup> Inclusion of thoracic impedance in Home Monitoring systems is therefore in the advanced experimental phase. Furthermore, since CRT-D and implantable cardioverter-defibrillator patients frequently suffer from non-cardiovascular comorbidities,<sup>2–4</sup> it may be reasonable to enable these devices to monitor non-cardiovascular parameters, such as potassium or glucose levels, to broaden the scope of clinical events that can be risk-stratified. Today's technological platform for automatic daily remote screening of device diagnostic data provides an exciting opportunity to design and constantly optimize increasingly sophisticated multiparameter predictive algorithms, and to prospectively evaluate their impact on patient outcomes, clinical burden, and health economic burden.

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**Conflict of interest:** S.S. has received research grants from Biotronik and is a member of the speaker's bureau of Biotronik. W.R.B. is a scientific advisor for Biotronik. H.N. has received speaker's honoraria from Biotronik. F.L. has been on Advisory Boards for Medtronic Inc and Sorin and has received research sponsorship from Medtronic Inc, Sorin, Biotronik, and St Jude Medical. V.P. and H.S. are currently local principal investigators in the ECHO-CRT trial, are members of the Steering Committee for the HOME-CARE study and receive honoraria for lectures and proctoring procedures. J.P. and S.B. are employees of Biotronik. C.M.W., A.K., C.S.B., and K.M., have nothing to declare.

## Appendix

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