ESC European Society of Cardiology

Europace (2023) **25**, 1–8
https://doi.org/10.1093/europace/euad062

CLINICAL RESEARCH

Dynamic changes in nocturnal heart rate predict short-term cardiovascular events in patients using the wearable cardioverter-defibrillator: from the WEARIT-France cohort study

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Received 12 December 2022; accepted after revision 31 January 2023

Aims While elevated resting heart rate measured at a single point of time has been associated with cardiovascular outcomes, utility of continuous monitoring of nocturnal heart rate (NHR) has never been evaluated. We hypothesized that dynamic NHR changes may predict, at short term, impending cardiovascular events in patients equipped with a wearable cardioverter-defibrillator (WCD).

Methods and results The WEARIT-France prospective cohort study enrolled heart failure patients with WCD between 2014 and 2018. Nighttime was defined as midnight to 7 a.m. NHR initial trajectories were classified into four categories based on mean NHR in the first week (High/Low) and NHR evolution over the second week (Up/Down) of WCD use. The primary endpoint was a composite of cardiovascular death and heart failure hospitalization. A total of 1013 [61 (interquartile range, IQR 53–68) years, 16% women, left ventricular ejection fraction 26% (IQR 22–30)] were included. During a median WCD wear duration of 68 (IQR 44–90) days, 58 patients (6%) experienced 69 events. After considering potential confounders, High-Up NHR trajectory was significantly associated with the primary endpoint compared to Low-Down [adjusted hazard ratio (HR) 6.08, 95% confidence interval (CI) 2.56–14.45, $P < 0.001$]. Additionally, a rise of >5 bpm in weekly average NHR from the preceding week was associated with 2.5 higher composite event risk (HR 2.51, 95% CI 1.22–5.18, $P = 0.012$) as well as total mortality (HR 11.21, 95% CI 3.55–35.37, $P < 0.001$) and cardiovascular hospitalization (HR 2.70, 95% CI 1.51–4.82, $P < 0.001$).

Conclusion Dynamic monitoring of NHR may allow timely identification of impending cardiovascular events, with the potential for 'preemptive' action.

Registration number Clinical Trials.gov Identifier: NCT03319160

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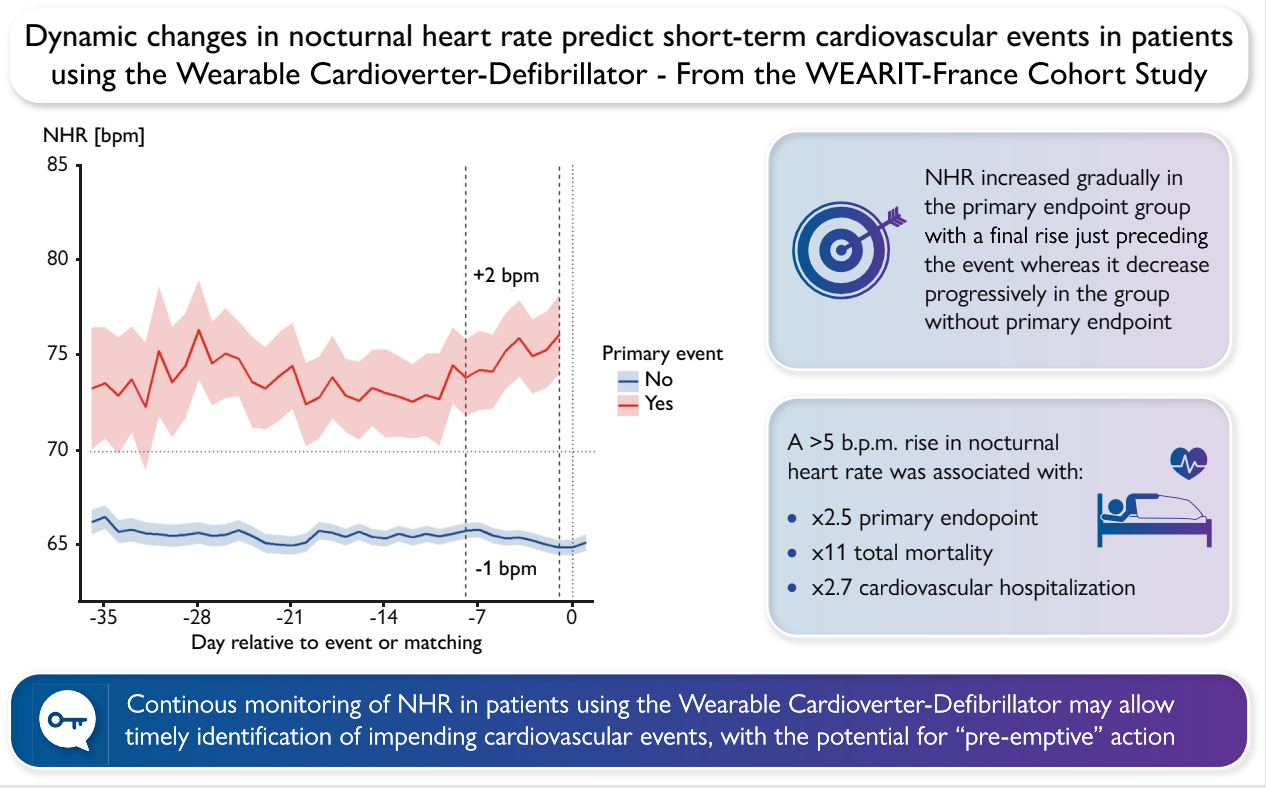
Graphical Abstract



Keywords Wearable cardioverter-defibrillator • Heart rate • Remote monitoring • Pre-emptive action • Heart failure

What's new?

- In patients equipped with wearable cardioverter-defibrillator, dynamic changes in nocturnal heart rate (NHR) were demonstrated to correlate in a temporal fashion with hard clinical endpoints such as cardiovascular death and hospitalization for heart failure.
- These observations suggest that longitudinal monitoring of NHR could be a valuable addition to the risk assessment arsenal for prediction of cardiovascular events, thereby opening avenues for *near-term* prevention.

Introduction

The past two decades have witnessed growing evidence for a strong relationship between high heart rate and adverse cardiovascular events.[1,2] The resting heart rate has often been inferred from ECGs done randomly at different times during the day, which may be subject to some variability, thereby introducing some deviation from a true resting state.[3] On the other hand, nocturnal heart rate (NHR) during sleep, being a state of true physiological rest, is likely to be a more accurate marker of resting heart rate, but has not been well studied as a prognostic risk marker. In addition, studies have traditionally relied on heart rate assessments at one fixed time point, often early in the course, to predict long-term outcomes.[4] However, similar to other risk markers, dynamic measurements of heart rate changes over time could improve the specificity of this marker and also potentially allow timely, specific pre-emptive action.

Using data from a large, nationwide cohort of patients with heart failure equipped with a wearable cardioverter-defibrillator (WCD) capable of recording all heart beats over the entire duration of use, we assessed whether dynamic monitoring of NHR allows timely identification of adverse cardiovascular events.

Methods

Study design and patient population

The WEARIT-France study (Clinical Trials.gov Identifier: NCT03319160) is a prospective nationwide cohort study assessing the use of the WCD in patients with heart failure across 88 French cardiology centres. The complete methodology has been described before.[5] This study complies with the Declaration of Helsinki and an ethics committee approved the research protocol. All patients who agreed to participate were entered into the study after having given their informed consent.

The wearable cardioverter-defibrillator

The WCD technology used in the WEARIT-France study is a commercially available external defibrillator (LifeVest, ZOLL Cardiac Management Solutions, PA), guided by an algorithm to detect ventricular tachyarrhythmia events.[6,7] The functioning of WCD has already been described[8,9] and current indications are summarized in the last guidelines.[10,11] During the index hospitalization when WCD therapy was initiated, the treating physician systematically assessed the appropriateness of WCD prescription and educated the patient regarding the transient risk for sudden cardiac death, functioning of the WCD, and benefits expected from the device. Additionally, just before discharge, a technical expert from the WCD company imparted 2 h of

practical education to the patient, encompassing the nature of the disease, indication for WCD, alarm management, and remote transmission. The local remote monitoring team monitored daily wear duration on a regular basis.

Collected data and study end points

At the time of enrolment, medical history, comorbidities, symptoms, and other baseline characteristics were collected in addition to the indication for WCD. The WCD is equipped with four electrodes allowing the calculation of heart rate based on the R–R intervals, which is computed as the mean of all the heart rate provided every 5 min. The WCD prescription period is 90 days in France and the observation period was therefore limited to this period.

The telemonitoring platform also allows for heart rate monitoring. We specifically focused on NHR, which was defined as the mean heart rate from midnight to 7 a.m. because of lower heart rate variability (see Supplementary material online, *Figure S1*). In addition, we monitored NHR changes over time. To analyse mid-term predictive value of *initial NHR trajectories* over the WCD use period, patients were classified into four groups (High-Up, High-Down, Low-Up, Low-Down) based on NHR trajectory using a cut-off mean of 70bpm during the first seven nights of use (High if ≥70 bpm or Low if <70 bpm) and then according to an increase (Up) or decrease (Down) of NHR between Week 1 and Week 2 (see Supplementary material online, *Figure S2*). Similar to previous publications,[1] mean cut-off of 70 bpm was determined because mean NHR was 68.8 (10.3) in this population. To assess the *short-term dynamics of NHR*, we defined ΔNHR as the difference between the weekly average NHR and that of the preceding week for each subject.

The primary endpoint was a composite of cardiovascular death and heart failure-related hospitalization. Endpoints were centrally adjudicated by an independent clinical events committee composed of three experts who adjudicated the events, by analysing the medical records/electrogram information, independent of each other and blinded to NHR and any additional information.

Statistical analysis

Preparation of this report was carried out in accordance with the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.[12] Descriptive statistics were used to report major clinical characteristics and frequency of events. Continuous variables are presented as mean (standard deviation) or median and interquartile range (IQR) where appropriate and compared with Welch's *t*-test or Wilcoxon–Mann–Whitney test. Nominal variables were expressed as number and percentage and compared using the Pearson's χ^2 test.

The time to event for each individual was defined from the first day of WCD wear to the day of first primary event, censoring, or end of follow-up (90 days), whichever came first. Cumulative incidence curves stratified by the *initial NHR trajectories* (High-Up, High-Down, Low-Up, Low-Down) were calculated by one minus the Kaplan–Meier estimator. Difference was assessed by the log-rank statistic. A multivariable Cox regression model with subjects' baseline characteristics as covariates was used to estimate the hazard ratios (HRs) of NHR initial trajectories for primary endpoint, adjusting on age, sex, body mass index, New York Heart Association class, left ventricular ejection fraction, prior hospitalization for heart failure, history of atrial fibrillation or kidney disease, and beta-blocker use.

Nocturnal heart rate dynamics were plotted in the primary endpoint and the non-primary endpoint groups to evaluate changes in trajectory over time. A nested case–control methodology was used matching 1 case for 7–9 controls to remove the effect of time since start of wear. In this way, on the day of an event (e.g. Day 14), a case is compared to a matched control of the same sex and on the same day of WCD wear.

To evaluate short-term dynamics of NHR (i.e. weekly changes in NHR), we used a prospective approach computing ΔNHR independently from the event. ΔNHR was defined as the difference between the weekly average NHR from 2 weeks back (W-2) and the week before (W-1) for each subject. Since a previous publication showed a significant HR increase in the last 10 days before an adverse cardiovascular event,[13] we assumed that a week represented adequate duration to reflect a clinically relevant change, but was not too long to miss any significant events. The ΔNHRs were updated weekly until the week just preceding the week of the event or until the end of observation period in case of no event (see Supplementary material online, *Figure S3*). ΔNHR was modelled as a continuous and a categorical covariate. The association between each endpoint and ΔNHR (W-1 minus W-2) as continuous covariates (per 5 bpm increase from W-2 to W-1) andcategorical covariate (change > 5 bpm from W-2 to W-1) was assessed by the Cox model[14,15] with adjustment for baseline NHR (2 weeks back: W-2) and for the confounders: age, sex, body mass index, New York Heart Association class, left ventricular ejection fraction, prior hospitalization for heart failure, history of atrial fibrillation or kidney disease, and beta-blocker use. The relationship between ΔNHR as a continuous variable and the HR for the primary endpoint was also examined by cubic spline curve with three knots, using a reference value of 60 bpm.

We performed sensitivity analysis among both genders, patients without history of atrial fibrillation and patients with New York Heart Association Class I and II, with respect to both mid-term NHR trajectories and short-term dynamics of NHR.

Analyses were performed using R software (version 4.1.3). All statistical tests performed were two-sided. A *P*-value of <0.05 was considered statistically significant. The proportional hazards assumption was tested and found satisfied.

Results

Baseline patient characteristics

Among 1157 patients enrolled in the WEARIT-France study, 1013 (88%) wore the WCD more than 2 weeks and were analysed. Clinical characteristics of the patients are listed in *Table 1*. The median age was 61 (IQR 53–68) years, 167 (16%) were females and median left ventricular ejection fraction was 26% (IQR 22–30). New York Heart Association status was Class I or II in 723 (71%) patients. A total of 76 (8%) patients had renal disease requiring therapy, 103 (10%) patients had history of atrial fibrillation, 71 (7%) had previous stroke. Regarding medical therapies, 905 (89%) patients were prescribed beta-blockers, 879 (87%) angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and 160 (16%) amiodarone.

Follow-up and primary endpoint evaluation

Median WCD wear time period was 68 (IQR 44–90) days in the overall patient population, with 58 (7%) patients experiencing events: 10 deaths (including 5 cardiovascular deaths) and 97 patients with cardiovascular hospitalizations (including 58 patients with heart failure-related hospitalizations) (*Table 2*).

At the end of wear time period, 548 (54.1%) received an implantable cardioverter-defibrillator, and left ventricular ejection fraction improved in 343 (33.9%). When comparing patients with and without event, 49.5 vs. 53.8%, respectively had an implantable cardioverter-defibrillator implantation and 4.1 vs. 35.9% had improved left ventricular ejection fraction (global *P*-value ≤ 0.001).

Initial nocturnal heart rate trajectories

Considering the whole population, the mean NHR was 68 ± 11 bpm during the first 2 weeks of WCD use and 64 ± 11 bpm during the last 2 weeks of WCD use ($P < 0.001$).

Looking at initial NHR trajectories classified into 4 groups (High-Up, High-Down, Low-Up, Low-Down), 123 (12%) patients were in the High-Up, 214 (22%) in the High-Down, 294 (30%) in the Low-Up, and 355 (36%) in the Low-Down group (27 patients were not classified because of missing NHR). The primary endpoint rate in the High-High group was significantly higher compared to the other groups (Log Rank $P < 0.001$; *Figure 1*). In multivariate Cox analysis, High-Up trajectory remained significantly associated with worse outcome [adjusted HR 6.08, 95% confidence interval (CI) 2.56–14.45; Low-Down as reference, $P < 0.001$] along with history of heart failure hospitalization

Table 1 Clinical characteristics of patients at baseline ($N = 1013$)

	All population ($N = 1013$)	No event ($N = 955$)	Event ($N = 58$)	*P*-value
Age, yrs	61 (53, 68)	61 (53, 68)	62 (54, 69)	0.505
Male sex, *N* (%)	846 (84)	800 (84)	46 (79)	0.374
BMI, kg/m^2	25.6 (23.1, 28.7)	25.6 (23.1, 28.7)	25.6 (23.4, 27.4)	0.720
NYHA class, *N* (%)				0.005
I and II	723 (71%)	691 (72%)	32 (55%)	
III and IV	290 (29%)	264 (28%)	26 (45%)	
Left ventricular ejection fraction, (%)	26 (22, 30)	26 (23, 30)	25 (20, 29)	0.104
Medical history, *N* (%)				
Myocardial infarction	830 (82%)	780 (82%)	50 (86%)	0.512
Valvular disease	129 (13%)	119 (12%)	10 (17%)	0.386
Atrial fibrillation	103 (10%)	95 (9.9%)	8 (14%)	0.347
Renal disease	76 (7.5%)	67 (7.0%)	9 (16%)	0.034
Stroke	71 (7.0%)	64 (6.7%)	7 (12%)	0.117
Medical therapy, *N* (%)				
Beta-blockers	905 (89%)	854 (89%)	51 (88%)	0.721
Diuretics	817 (81%)	767 (80%)	50 (86%)	0.270
ACE-I/ARBs	879 (87%)	837 (88%)	42 (72%)	<0.001
Amiodarone	160 (16%)	147 (15%)	13 (22%)	0.155

Data are presented as *n* (%) or mean ± SD.
ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; NYHA, New York Heart Association.

Table 2 Summary of events

	Patients, $N = 1013$	Events
Death	**10 (1.0)**	**10**
- Cardiovascular cause	5 (0.5)	5
- Non-cardiovascular cause	5 (0.5)	5
Hospitalization	**133 (13)**	**160**
- Cardiovascular hospitalization	97 (9.6)	112
Hospitalization for heart failure	58 (5.6)	64
Other cardiovascular hospitalization	44 (4.3)	48
- Non-cardiovascular hospitalization	45 (4.4)	48

Lines in bold are event categories. Lines preceded by " - " (such as " - Cardiovascular cause ") are subcategories of the event in bold.

(HR 2.26, 95% CI 1.25–4.10, $P = 0.007$), whereas angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use was associated with lower occurrence of primary endpoint (HR 0.30, 95% CI 0.16–0.57, $P < 0.001$). In sensitivity analyses, the risk associated with a High-Up trajectory was confirmed in both sexes, in patients without history of atrial fibrillation, and in patients with New York Heart Association Class I and II [HR 95% CI 6.09 (2.25–16.50), $P < 0.001$ for males, 8.85 (1.21–64.63), $P = 0.032$ for females; 5.58 (2.22–14.05), $P < 0.001$ for patients without atrial fibrillation, 8.75 (2.28–33.62), $P = 0.002$ for New York Heart Association Class I and II].

Short-term dynamics of nocturnal heart rate

Heart rate dynamics according to the primary endpoint are represented in *Figure 2*. In the group with cardiovascular events, NHR increased starting 7 to14 days before the event, whereas it decreased progressively in the group without primary endpoint. In the last 7 days before the event (from −8 to −1 day), NHR increased by +2 bpm (IQR −3; + 6) in the group with primary endpoint, whereas it decreased by −1 (IQR −1; −1) in the non-event group (*Figure 2*).

The distribution of ΔNHR is graphically shown in Supplementary material online, *Figure S4*. Most patients had only minimal change in NHR from the preceding week [median ΔNHR—0.44 bpm (IQR −2.44; 1.53)] during the WCD wear period. The restricted cubic spline model showed that increase in ΔNHR correlated linearly with higher risk for primary endpoint (*Figure 3*).

The association between individual components of the primary endpoint and NHR at the first night of WCD use as well as ΔNHR is summarized in *Table 3*. As a continuous covariate, both NHR at first night and ΔNHR were associated with total mortality and cardiovascular hospitalization. When considering ΔNHR as a continuous variable, each 5 bpm increase in ΔNHR was associated with a 41% higher risk of adverse events. This association was even stronger when considering ΔNHR as a categorical variable; an increase of ΔNHR > 5 bpm was associated with a 2.5-fold higher risk of primary endpoint (HR 2.51, 95% CI 1.22–5.18, $P = 0.012$), an 11-fold higher risk of death (HR 11.21, 95% CI 3.55–35.37, $P < 0.001$), and an almost three-fold higher risk of cardiovascular hospitalization (HR 2.70, 95% CI 1.51–4.82, $P < 0.01$). When considering subgroup analysis, similar results were obtained in males and females. In patients without history of atrial fibrillation, an increase of ΔNHR > 5 bpm was associated with two-fold higher risk of primary endpoint (HR 2.51; 95% CI 1.16–5.40, $P = 0.019$). Regarding patients with New York Heart Association

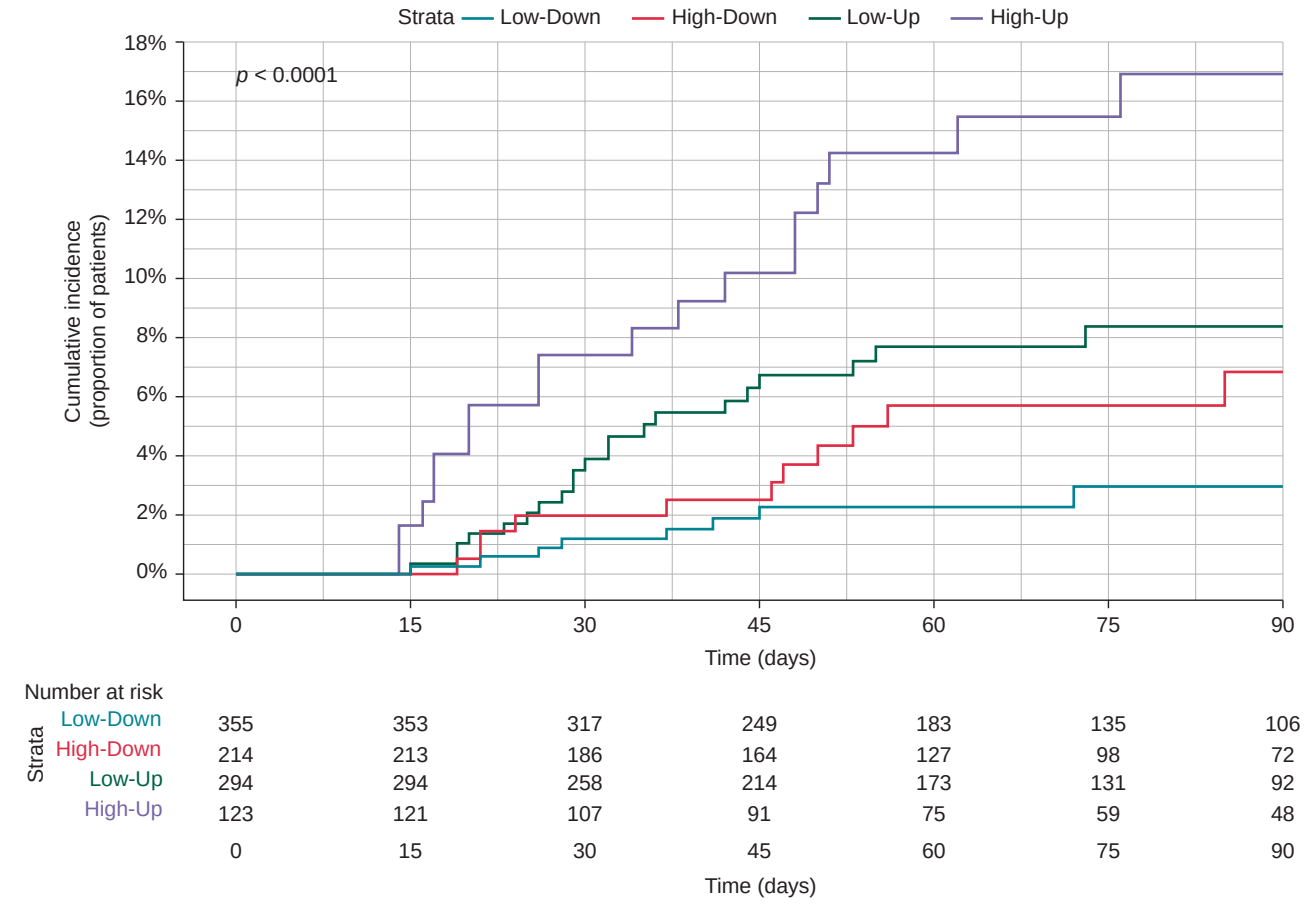


Figure 1 Primary endpoint cumulative incidence according to initial NHR trajectories. NHR, nocturnal heart rate.

Class I and II, an increase of NHR ≥ 5 as compared to the previous week was associated with point estimates for HR > 2 but was not significant due to loss of power.

Discussion

In this study, we found that NHR was associated with adverse cardiovascular events in a heart failure population within a short- to mid-term timeframe. Moreover, dynamic changes in NHR were demonstrated to correlate in a temporal fashion with hard clinical endpoints such as cardiovascular death and hospitalization for heart failure. Weekly rise of NHR > 5 bpm was especially associated with high risk, suggesting potentially actionable cut-offs for clinical application. While needing further validation in future studies, these observations suggest that NHR, especially with longitudinal monitoring, could be a valuable addition to the risk assessment arsenal for prediction of cardiovascular events.

Prediction of cardiovascular events

Because of the high rate of re-hospitalizations, high mortality, poor quality of life, and the substantial cost sustained by national healthcare systems, much effort has been made to identify the parameters/risk factors that can effectively contribute to prediction and prevention of decompensation events and hospitalizations in patients with heart failure.[16] Previous studies showed that heart rate was another parameter associated with adverse outcome in different settings, especially in heart failure.[17] Nevertheless, prediction of cardiovascular events with 'static' heart rate assessment, reflecting one-time status, has limitations as it can be affected by a number of factors, potentially affecting specificity. In addition, event risk is a dynamic, time-varying phenomenon; therefore, it makes sense that continuous measurements would be preferable to a single one.[18] In this regard, dynamic monitoring holds promise, wherein each patient serves as his/her own control and changes over time may yield higher sensitivity as well as specific risk assessment. Vazir *et al.*[4] reported that, compared to the previous visit, an increase >5 bpm in resting heart rate was associated with 1.06 times higher risk of cardiovascular death or hospitalization for heart failure. However, HR assessment was irregular as it was evaluated at any time from every 2 weeks to every 4 months. A closer and automated measurement of heart rate over time, as in this study, could identify events with better accuracy and in a timely manner to avoid hospitalization or death. We assessed the mean NHR weekly and found that an increase of > 5 bpm was associated with a more than two-fold risk of cardiovascular death or hospitalization for heart failure.

Remote monitoring and connected devices

Telemedicine can allow for remote monitoring and management of patients with chronic cardiovascular diseases, making it possible to assess medication adherence and detecting early signs of decompensation before it results in additional complications or hospital readmission. Even though this has mostly been done with invasive devices,[19] advances in technology now make it possible to use non-invasive solutions.[20,21]

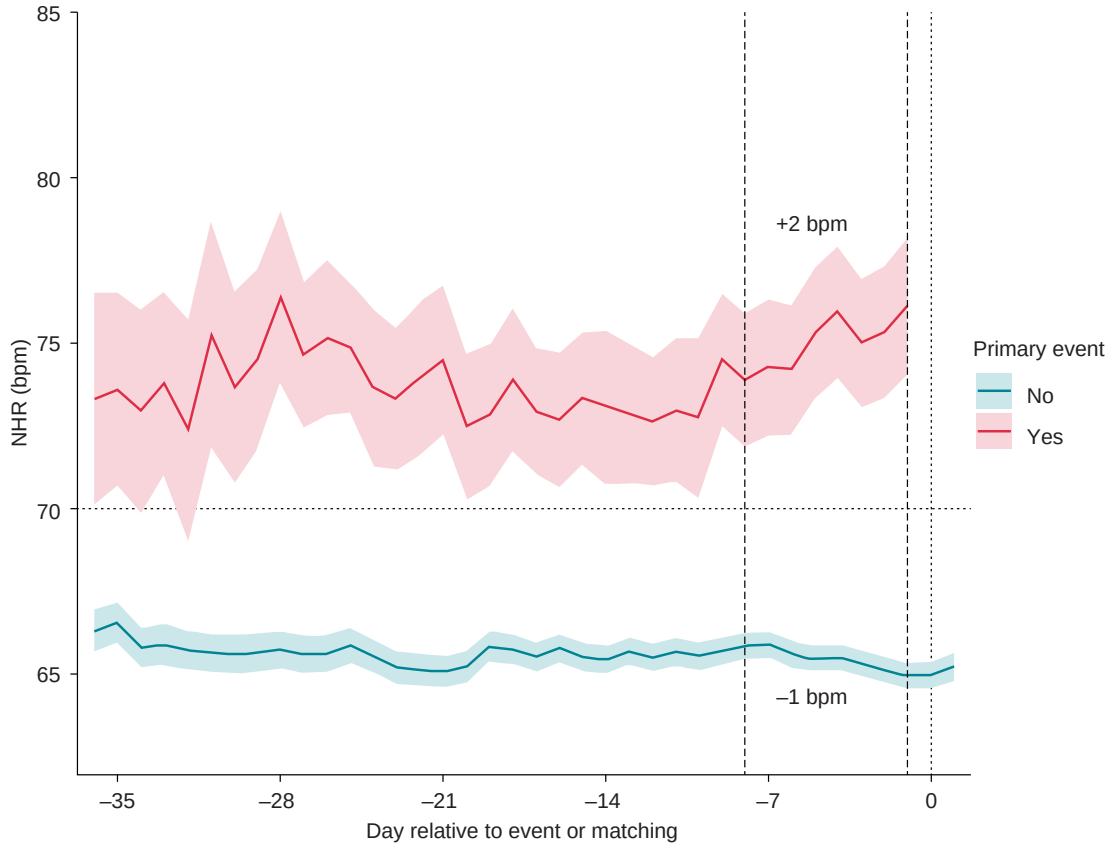


Figure 2 NHR dynamics among patients with and without primary event. NHR, nocturnal heart rate.

Moreover, the large population of patients with implanted and wearable devices (such as implantable cardioverter-defibrillator, cardiac resynchronization therapy and WCD) with rapid expansion of remote monitoring technology presents an important opportunity, which needs to be leveraged to improve risk prediction.

To the best of our knowledge, this work is the first to use heart rate collected in an automatic and continuous manner. Indeed, in prior work attempting to predict cardiovascular events, heart rate was measured manually or derived from a single 12 lead ECG.[4,13,22] While we studied a selected population of patients equipped with a WCD, signal acquisition is becoming easier with the recent development of a wide range of connected devices,[23] which have become deeply entrenched in our daily lives. Despite the promise of remote patient monitoring, this technology has thus far remained relatively underutilized. In the era of artificial intelligence, remote and increasingly personalized patient care, one can imagine that heart rate could be monitored with a simple connected watch, greatly expanding the applicability of this concept.[24] With such connected devices, continuous data acquisition has the potential to open up avenues for *near-term* prevention, where dynamic changes in monitored parameters can be used to take corrective, 'pre-emptive' action, avoiding adverse events.

Near-term prevention

Long-term risk prediction is often disappointing with imperfections in risk assessment as well as solutions (for instance, an implantable cardioverter-defibrillator along with its side effects).[25,26] *Near-term prevention*, which relies upon prompt action in response to warning signs, could allow timely intervention to avoid the adverse outcome but without the inconvenience of 'permanent' therapy.[27] In fact, cardiovascular risk is dynamic and modulated by a variety of environmental factors, seasonal variations, and circadian rhythms.[28] In the present study, we have demonstrated that dynamic monitoring of NHR has the potential to be not only a reliable predictor of cardiovascular events in patients with heart failure but could also pave the way towards near-term prevention of cardiovascular events. Underlying mechanisms for heart rate increase before the event remain to be fully elucidated and compensatory tachycardia in response to volume overload could be one of the possible mechanisms. Nonetheless, the important point is that the NHR rise preceded major events such as hospitalization or death by a time period which appears reasonably sufficient for timely clinical intervention. One can imagine that in the future, combining clinical characteristics and remote monitoring will allow to identify specific groups at risk of coronary event or heart failure acutization or maybe sudden cardiac arrest. Therefore, we will be able to pre-empt these events and take specific measures.

Limitations

In this study, we have presented novel findings that may help refine use of heart rate as a marker to eventually improve short-term prediction and survival in heart failure populations; however, we need to acknowledge some limitations. First, this work should be viewed as a proof-of-concept study, as heart rate was collected using a WCD with limited follow-up, and may be not applicable to the entire heart failure population. However, as already mentioned, similar information is obtainable for other implanted devices and wearable sensors; as a result, this approach can be further tested and expanded in the future. Our study population consisted mainly in patients with ischaemic cardiomyopathy, so caution has to be exercised in extrapolating results to other

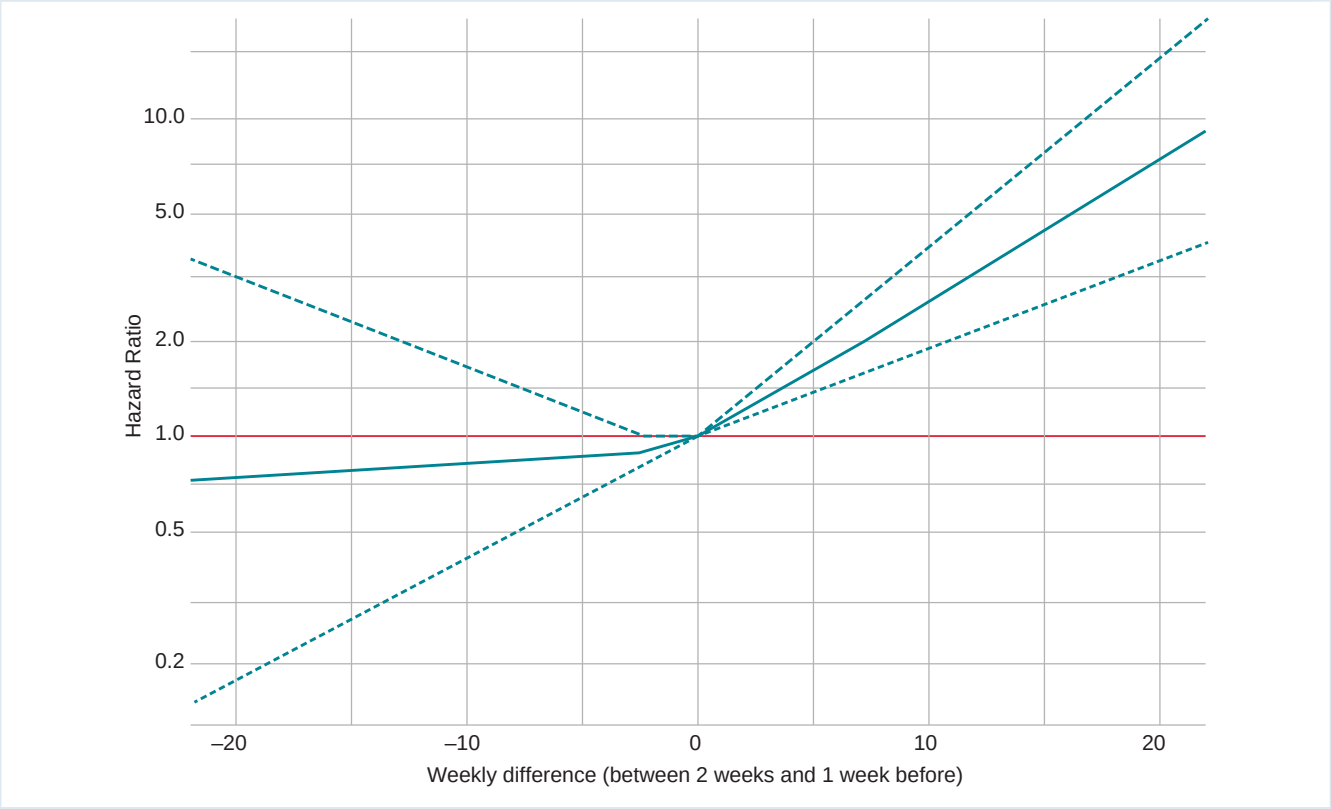


Figure 3 Association between ΔNHR and primary endpoint occurrence. NHR, nocturnal heart rate.

Table 3 Association between NHR covariates and outcomes

	Continuous analysis		Continuous analysis		Categorical analysis	
	NHR at first night of WCD use (per 5 bpm increase)		Δ NHR (per 5 bpm increase)		Δ NHR increase > 5 bpm	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Cardiovascular death or heart failure hospitalization	1.23 (1.13–1.35)	<0.001	1.41 (1.13–1.77)	0.003	2.51 (1.22–5.18)	0.012
All death	1.28 (1.04–1.56)	0.023	1.64 (1.15–2.36)	0.007	11.21 (3.55–35.37)	<0.001
Cardiovascular hospitalization	1.14 (1.05–1.23)	0.015	1.42 (1.18–1.70)	<0.001	2.70 (1.51–4.82)	<0.001

bpm, beats per minute; HR, hazard ratio; NHR, nocturnal heart rate; WCD, wearable cardioverter-defibrillator.

causes of heart failure. Moreover, a high proportion of the patients were on beta-blockers; whether the magnitude of risk associations would be different in patients not on heart rate modulating drugs warrants further evaluation. Finally, further work is needed to confirm the associations reported in this study as well as the effectiveness of a strategy based on NHR monitoring to reduce hospitalization and mortality.

Conclusions

In patients with WCD, continuous dynamic monitoring of NHR helps to predict adverse cardiovascular events. It holds promise as a means of improving risk prediction prior to timely pre-emptive action, enabling reduction of adverse outcomes in populations at risk.

Supplementary material

Supplementary material is available at *Europace* online.

Acknowledgements

We deeply thank all the investigators of the WEARIT-France Study: Laurence Guedon Moreau, Mohanad Mahfoud, Philippe Ritter, Jean Marc Dupuis, Arab Yalioua, Antoine Dompnier, Marc Goralski, Saïda Cheggour,

Christophe Leclercq, Eloi Marijon, Jérôme Bouet, Clémentine André, Fabrice Extramiana, Florent Briand, Anne Rollin, Gilles Lande, Philippe Chevalier, Jean-Luc Pasquié, Nicolas Lellouche, Bruno Degand, Yves Cottin, François Jourda, Jacques Mansourati, Angeline Martin, Antoine Da Costa, Olivier Billon, Isabelle Cheradame, Jean-Sylvain Hermida, Julien Bayard, Romain Eschalier, Benoit Guy Moyat, Vladimir Manenti, Hervé Gorka, Nicolas Combes, Antoine Milhem, Olivier Piot, Yves Guyomar, Renaud Fouché, Elisabeth Somody Litoux, Anne Quentin, Jean Baptiste Berneau, Thierry Tibi, Aurélien Miralles, Fiorella Salerno, Peggy Jacon, Laurentin Nitu, Damien Brunet, Hugues Bader, Arnaud Savoure, Pascal Sagnol, Frédéric Sebag, Sebastien Buffler, Joël Fedida, Julien Pineau, Guillaume De Geeter, Adlane Zemmoura, Ahmed Salhi, Eric Verbrugge, Sophie Pynn, Jean Pierre Gueffet, Walid Amara, Aurélien Seemann, Pierre Winum, Nicolas Johnson, Claire Vanesson, Alexis Mechulan, Vincent Hugon, Xavier Marchand, Jean-Claude Deharo, Sylvain Reuter, Raphael Sandras, Damien Legalloi, Olivier Garrier, Gaël Jauvert, Jérémy Descoux, Hugues Blangy, Alain Lebon, Pierre Sultan, Franck Sibellas, Samer Mousi, Gabriel Laurent, Maxime Pons, Halim Marzak, Jérôme Clerc, Hassan Barake, Aurélie Guiot, Vincent Algalarrondo, Laurent Palud, Denis Raguin, Frédéric Treguer, Pierre Le Franc, Isabelle Lecardonnel, Frederic Fossati, Ghassan Moubarak, Omar Bilel Mokrani, Pascal Chavernac. We gratefully thank Nobutaka Murata and Nicole Bianco of ZOLL for providing the technical assistance for data analysis.

Funding

This work was supported by the Institut National de la Santé et de la Recherche Médicale (INSERM) and Zoll Medical Corporation.

Conflict of interest: E.M. is consultant for ZOLL, Boston, Medtronic and received unrestricted grants from industrial partners (Medtronic, Abbott, Boston Scientific, Microport, Biotronik and ZOLL). R.G. have been compensated by ZOLL for giving presentations. The remaining authors have nothing to disclose.

Data availability

The data underlying this article will be shared on reasonable request to ZOLL.

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