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ORIGINAL RESEARCH

Heart Rate Variability Triangular Index as a Predictor of Cardiovascular Mortality in Patients With Atrial Fibrillation

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BACKGROUND: Impaired heart rate variability (HRV) is associated with increased mortality in sinus rhythm. However, HRV has not been systematically assessed in patients with atrial fibrillation (AF). We hypothesized that parameters of HRV may be predictive of cardiovascular death in patients with AF.

METHODS AND RESULTS: From the multicenter prospective Swiss-AF (Swiss Atrial Fibrillation) Cohort Study, we enrolled 1922 patients who were in sinus rhythm or AF. Resting ECG recordings of 5-minute duration were obtained at baseline. Standard parameters of HRV (HRV triangular index, SD of the normal-to-normal intervals, square root of the mean squared differences of successive normal-to-normal intervals and mean heart rate) were calculated. During follow-up, an end point committee adjudicated each cause of death. During a mean follow-up time of 2.6±1.0 years, 143 (7.4%) patients died; 92 deaths were attributable to cardiovascular reasons. In a Cox regression model including multiple covariates (age, sex, body mass index, smoking status, history of diabetes mellitus, history of hypertension, history of stroke/transient ischemic attack, history of myocardial infarction, antiarrhythmic drugs including β blockers, oral anticoagulation), a decreased HRV index ≤ median (14.29), but not other HRV parameters, was associated with an increase in the risk of cardiovascular death (hazard ratio, 1.7; 95% CI, 1.1–2.6; *P*=0.01) and all-cause death (hazard ratio, 1.42; 95% CI, 1.02–1.98; *P*=0.04).

CONCLUSIONS: The HRV index measured in a single 5-minute ECG recording in a cohort of patients with AF is an independent predictor of cardiovascular mortality. HRV analysis in patients with AF might be a valuable tool for further risk stratification to guide patient management.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02105844.

Key Words: atrial fibrillation ■ heart rate variability ■ morbidity/mortality

Atrial fibrillation (AF) is the most common arrhythmia with rising incidence and is associated with a high risk for stroke, congestive heart failure (CHF), and death compared with the general population.[1–5] Therefore, risk stratification in patients with AF is of high clinical importance.

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For Sources of Funding and Disclosures, see page 9.

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CLINICAL PERSPECTIVE

What Is New?

- Heart rate variability (HRV) can be assessed in routine ambulatory 5-minute ECG recordings in patients with AF.
- Out of various conventional HRV parameters, HRV triangular index is an independent predictor of cardiovascular and all-cause mortality in a cohort of patients with AF.
- To date, this is the largest study assessing the prognostic implications of impaired HRV in patients with AF.

What Are the Clinical Implications?

- Prognostic information regarding mortality risk can be derived from the functional status of the cardiac autonomic nervous system in patients with AF.
- Impairment of HRV triangular index identifies high-risk patients with AF.
- Short-term HRV analysis is a simple diagnostic tool that is widely available at low cost and allows noninvasive risk stratification in patients with AF.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
CHF	congestive heart failure
HR	hazard ratio
HRV	heart rate variability
HRVI	heart rate variability triangular index
MI	myocardial infarction
NN	normal-to-normal
SR	sinus rhythm

There is a large body of evidence that important prognostic information regarding mortality risk can be derived from the functional status of the cardiac autonomic nervous system.[6–14] Noninvasive assessment of the cardiac autonomic status can be achieved by the analysis of heart rate variability (HRV). In sinus rhythm (SR), depressed HRV has been associated with poor prognosis, in particular after myocardial infarction (MI)[6–10,15–18] and CHF.[11–14,19] However, in patients with AF, there are very limited data on the association of HRV and death. Nevertheless, cardiac autonomic dysfunction has also been linked to AF because the atria have a strong autonomic innervation.[20,21] Furthermore, the AV node is highly susceptible to input from the autonomic nervous system.[22–26] Temporal changes in autonomic regulation have been shown to precede the onset of AF.[27,28] In addition, autonomic nerve activity plays an important role in the maintenance of AF, and modulating autonomic nerve function contributes to AF control.[29–35]

Based on these findings, we hypothesize that impaired HRV may be predictive of cardiovascular death and other adverse outcomes in patients with AF. The Swiss-AF (Swiss Atrial Fibrillation) Cohort Study offers the unique opportunity to study the association of HRV and mortality in a large, unselected but well-defined cohort of patients with AF.

METHODS

A provision of the consent forms, as approved by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz), does not allow data to be made publicly available. Researchers may contact the authors for the potential submission of research proposals for future analyses.

Patient Population

Patients of the ongoing prospective, multicenter observational Swiss-AF cohort study performed in 14 sites across Switzerland were included in this study. Detailed information of the study design and size has been published previously.[36] In the Swiss-AF cohort study, a history of previously documented AF was required for inclusion. The main exclusion criteria were the presence of exclusively short, reversible AF episodes (eg, in sepsis or postoperatively) and acute illness of any cause within the past 4 weeks.

Of the 2415 patients enrolled in the Swiss-AF study, we excluded 14 patients because of missing baseline ECGs and 38 patients because of low-quality ECGs (Figure 1). After analysis of the baseline rhythm, we excluded 360 patients (14.9%) with paced atrial and/or ventricular rhythm, 34 with atrial flutter, 6 with atrial tachycardia, 5 with junctional rhythm, 1 with a constant switch between atrial bursts and SR, and 1 with pleomorphic premature ventricular contractions. Furthermore, we excluded 34 patients because of any missing and/or incomplete follow-up information or because of withdrawal of informed consent. Thus, 1922 (79.6%) patients remained in the present analysis. The Swiss-AF study has been approved by local ethics committees in the participating centers; each participant gave written informed consent.

Clinical Measures

Standardized case report forms were used to obtain information on personal characteristics, risk factors, comorbidities, conventional pharmacological and interventional treatment, and other factors. At baseline,

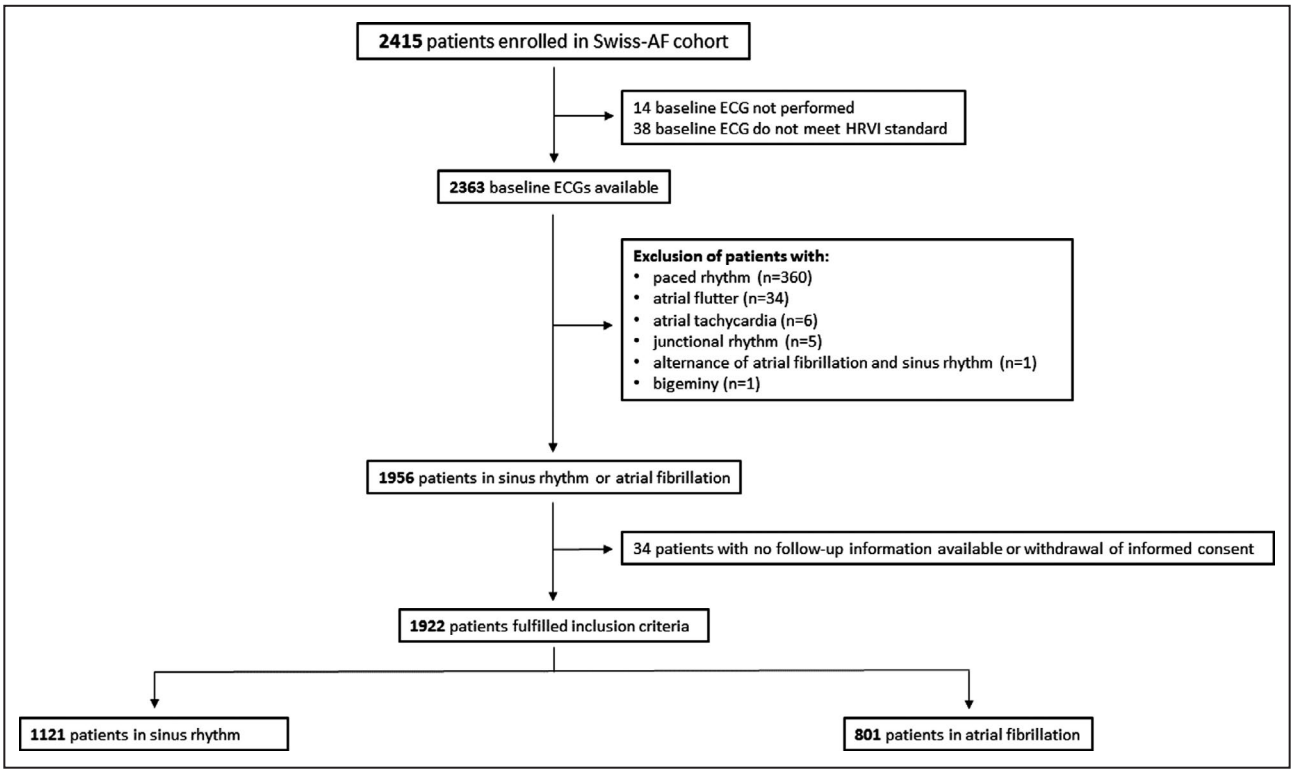

Figure 1. Flow chart of patient selection from the Swiss Atrial Fibrillation (Swiss-AF) Cohort Study.
HRVI indicates heart rate variability triangular index.

body height and weight were measured to calculate body mass index.

Assessment of HRV Parameters

At enrollment, all patients underwent a high-resolution 16-lead resting ECG recording for at least 5 minutes (CS-200 Excellence and CS-200 Touch, Schiller AG, Baar, Switzerland). All ECG recordings were saved with a sampling frequency of 1 kHz (signal bandwidth 0.04–387 Hz) and a resolution of 1 μV/bit. The high sampling frequency (twice as high as standard ECG devices) allowed state-of-the art bio-signal processing analyses during SR and AF. All collected recordings were saved in a central ECG core laboratory at the Cardiocentro in Lugano, Switzerland.[36] The following parameters of HRV were calculated according to previously published methods and by use of customized and validated software[37]: heart rate variability triangular index (HRVI), SD of the normal-to-normal (NN) intervals, square root of the mean squared differences of successive NN intervals, and mean heart rate. For calculation of the HRVI, all NN intervals were first divided according to their length in bins of ≈8 ms (precisely 7.8125 ms=1/128 seconds). Then the number of NN intervals in the modal bin (ie, the maximum of the density distribution) was sought. Finally, the HRVI was defined as the total number of NN intervals divided by the number of NN intervals in the modal bin (Figure 2).[37]

Outcome Measurements

Follow-up investigations were performed on a yearly basis for assessment of clinical events. Every visit was performed at the reference local study center. If patients could not attend an appointment (eg, because of their medical condition), each study center offered them either a home visit or a telephone interview. The primary end point of this analysis was cardiovascular death. Secondary end points were defined as follows: all-cause mortality, MI, ischemic stroke, bleeding (major and clinically relevant nonmajor bleeding), and hospitalization as a result of CHF. Details on the definition of secondary end points can be found in Data S1. Clinical events were adjudicated by 2 investigators. If there was a discrepancy between the 2 investigators (eg, regarding the cause of death), a third investigator reviewed the event.

Statistical Analysis

Baseline characteristics were categorized according to the patient's baseline rhythm (SR versus AF). Continuous variables are presented as mean±SD and were analyzed using the *t* test. Categorical variables

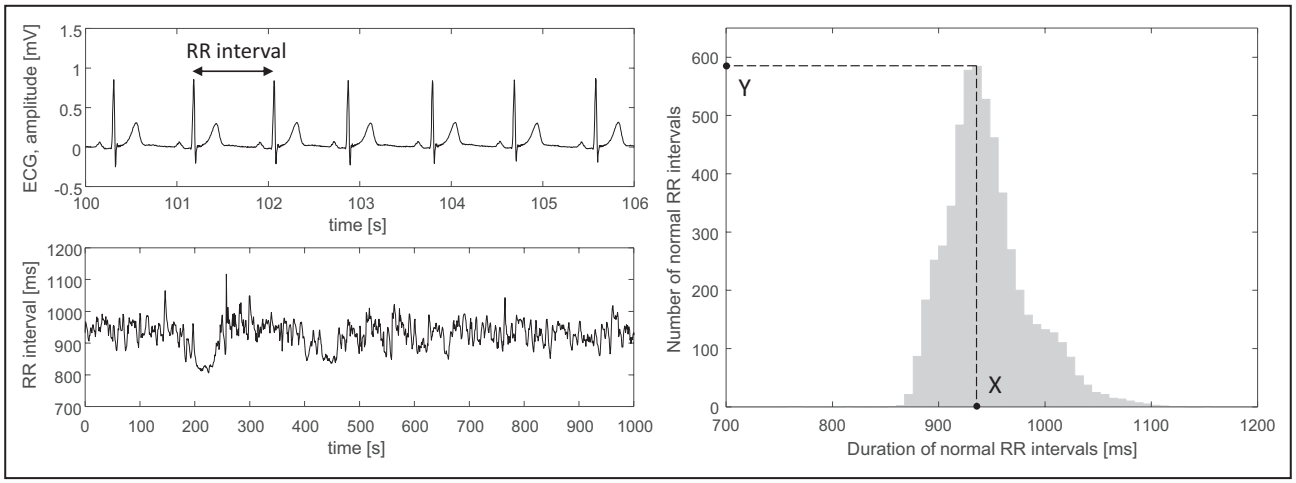

Figure 2. Calculation of heart rate variability triangular index (HRVI).
Left upper figure: Standard resting ECG recording. Left lower figure: Corresponding tachogram of the RR intervals. Right figure: Calculation of HRVI. First, all normal-to-normal (NN) intervals are divided according to their length in bins of 8 ms. Second, the number of NN intervals in the modal bin (ie, the maximum of the density distribution) is sought. Finally, the HRVI is defined as the total number of NN intervals divided by the number of NN intervals in the modal bin. X indicates the modal bin; and Y, the number of NN intervals in the modal bin.

are expressed as counts (percentages) and were compared using the chi-square test. Correlations between variables were assessed by Spearman rank correlation. We investigated the association of HRV parameters with the primary and secondary end points using Cox proportional hazard models. We built a bivariable Cox regression model (adjusted for age) and a multivariable Cox regression model (additionally adjusted for sex, body mass index, smoking status, history of diabetes mellitus, history of hypertension, history of stroke/transient ischemic attack, history of MI, antiarrhythmic drugs [class Ic and III] including β blockers and oral anticoagulants) to test each of the HRV parameters in turn. To examine the effect of each HRV parameter, we dichotomized it to low or high. Because of the lack of widely accepted cut-offs in AF cohorts,[37–39] we used each parameter's observed median as our cut-off. Mortality rates were estimated by the Kaplan–Meier method. Hazard ratios (HRs) are presented with 95% CIs. Possible effect modifications (interactions) were tested by including interaction terms to the proportional hazard models. Statistical analyses were performed using SPSS IBM SPSS Statistics for Windows, Version 25 (IBM Corp., Armonk, NY) and SAS 9.4 (SAS Corporation, Cary, NC).

RESULTS

Of the 1922 patients included in the present analysis, 1121 patients were in SR (58%) and 801 patients (42%) were in AF at the time of baseline ECG recording (Table 1). Patients in AF were older (75±8 versus 71±8 years), had a higher prevalence of hypertension (75% versus 65%), diabetes mellitus (21% versus 13%), prior history of CHF (33% versus 16%), MI (17% versus 12%), stroke or transient ischemic attack (25% versus 17%), were more often treated with vitamin K antagonists (53% versus 26%), and received direct oral anticoagulants less often (41% versus 61%). Pulmonary vein isolation and electrocardioversion had been performed more often in patients in SR at baseline (34% versus 6% and 38% versus 33%, respectively).

Measures of HRV showed important, even rather weak, correlations with clinical variables of the study cohort (Table S1). In particular, all HRV parameters correlated with age and CHA_2DS_2-VASc score, but not with sex. HRVI also correlated with systolic and diastolic blood pressure and with AF symptoms.

During a mean follow-up of 2.6±1.0 years, 143 patients (7.4%) died. The cause of death was cardiovascular in 92 patients (cumulative incidence rate of 1.87 per 100 patient-years). Compared with survivors, nonsurvivors were older (77±8 versus 72±8 years); were less frequently women (20% versus 28%; had a higher prevalence of hypertension (78% versus 68%), diabetes mellitus (36% versus 15%), prior CHF (48% versus 21%), and MI (21% versus 14%); had a higher CHA_2DS_2-VASc score (4.4±1.6 versus 3.3±1.7); received vitamin K antagonists (55% versus 36%) more often; and were less often treated with antiarrhythmic drugs (18% versus 29%) and direct oral anticoagulants (32% versus 54%).

Using a Cox proportional hazard model and adjusting for age, the HRVI ≤ median, but not other HRV parameters, was associated with an increase in cardiovascular mortality (hazard ratio [HR], 1.71; 95% CI;

Table 1. Characteristics of Patients Grouped by Baseline Rhythm

Characteristic	All Patients (N=1922)	Patients in SR (N=1121)	Patients in AF (N=801)
Age, y	73±8	71±8	75±8
Female sex, N (%)	532 (28)	351 (31)	181 (23)
Body mass index	27.7±4.9	27.3±4.8	28.3±4.9
Systolic/diastolic blood pressure, mm Hg	135±19/78±12	136±18/77±11	133±18/79±13
History of hypertension, N (%)	1325 (69)	725 (65)	600 (75)
History of diabetes mellitus, N (%)	311 (16)	147 (13)	164 (21)
Active and former smokers, N (%)	1080 (56)	626 (56)	454 (57)
History of electrocardioversion, N (%)	692 (36)	429 (38)	263 (33)
History of PVI, N (%)	425 (22)	375 (34)	50 (6)
History of myocardial infarction, N (%)	271 (14)	135 (12)	136 (17)
History of clinical stroke or TIA, N. (%)	384 (20)	188 (17)	196 (25)
History of heart failure, N (%)	446 (23)	184 (16)	262 (33)
CHA_2DS_2-VASc score	3.4±1.7	3.0±1.7	3.8±1.7
Antiarrhythmic therapy (class Ic and III)	535 (28)	343 (31)	192 (24)
β blockers, N (%)	1294 (67)	724 (65)	570 (71)
Direct oral anticoagulants, N (%)	1012 (53)	682 (61)	330 (41)
Vitamin K antagonists, N (%)	714 (37)	289 (26)	425 (53)

Data are means±SD or counts (percentages). AF indicates atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke or TIA or thromboembolism (2 points), vascular disease, age 65–74 years, female sex; PVI, pulmonary vein isolation; SR, sinus rhythm; and TIA, transient ischemic attack.

1.13–2.60; *P*=0.01; Figure 3). This association remained similar after additionally adjusting for sex, body mass index, smoking status, history of diabetes mellitus, history of hypertension, history of stroke or transient ischemic attack, history of MI, antiarrhythmic drugs, β blockers, oral anticoagulants (HR, 1.70; 95% CI, 1.12–2.59; *P*=0.01; Table 2).

We also found all-cause mortality to be higher for patients with HRVI ≤ median when adjusting for age l (HR, 1.48; 95%CI, 1.06–2.01; *P*=0.02). The direction and strength of the association remained the same also, when adjusting for the other potential confounders (HR, 1.42; 95% CI, 1.02–1.98; *P*=0.04). We found no strong evidence for HRVI or any other HRV measure to be associated with any of the secondary end points, such as MI, ischemic stroke, bleeding (major and clinically relevant nonmajor bleeding), and hospitalizations caused by CHF (Table 3).

Subgroup analyses are shown in Figure 4. Interaction tests provided no support for different associations of HRVI with cardiovascular mortality depending on the grouping variables, particularly not when stratified by

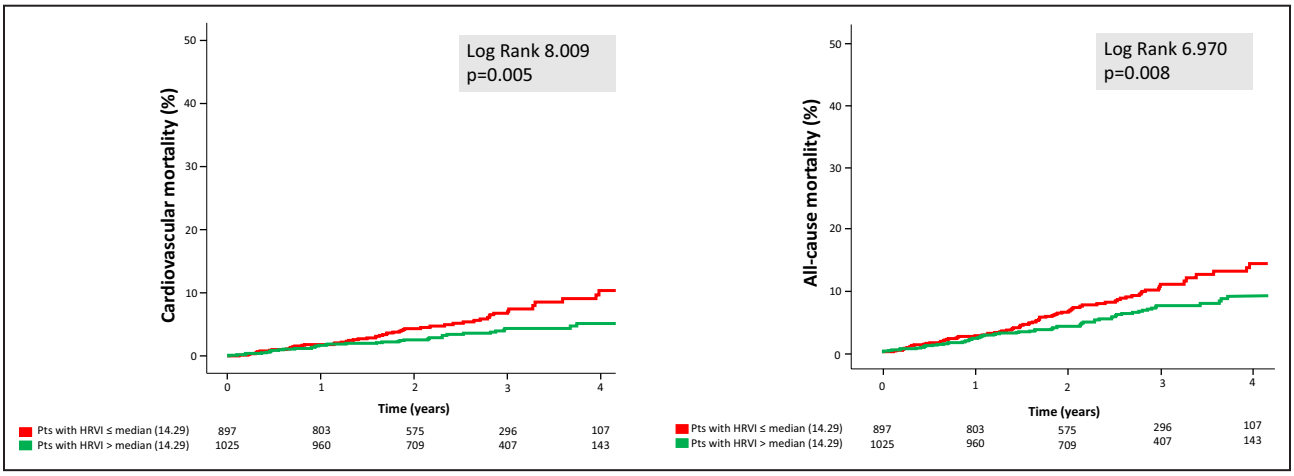

Figure 3. Prognostic impact of heart rate variability triangular index (HRVI) in the entire study cohort.
Kaplan–Meier curves of cardiovascular and all-cause mortality stratified by the median heart rate variability triangular index. Mortality probabilities were significantly different (*P*=0.005 and *P*=0.008, respectively). Pts indicates patients.

Table 2. Cox Proportional Hazard Models for Cardiovascular Mortality

Parameter	No. of Events	Incidence/100 atient Years	Bivariable Model HR (95% CI)	*P* Value	Multivariable Model HR (95% CI)	*P* Value
HRVI						
HRVI >median	37	0.75	Ref.		Ref.	
HRVI ≤ median	55	1.12	1.71 (1.13–2.60)	0.01	1.70 (1.12–2.59)	0.01
SDNN						
SDNN >median	46	0.93	Ref.		Ref.	
SDNN ≤ median	46	0.93	1.09 (0.72–1.64)	0.68	1.11 (0.74–1.67)	0.62
RMSSD						
RMSSD > median	50	1.02	Ref.		Ref.	
RMSSD ≤ median	41	0.83	1.03 (0.68–1.56)	0.88	1.05 (0.69–1.61)	0.81
MHR						
MHR >median	61	1.24	Ref.		Ref.	
MHR ≤ median	31	0.63	0.67 (0.43–1.03)	0.07	0.67 (0.438–1.05)	0.08

Data are hazard ratios (HRs) (95% CIs). *P* values were based on Cox proportional hazard models. Bivariable model was adjusted for age. Multivariable model was additionally adjusted for sex; body mass index; smoking status; history of diabetes mellitus; history of hypertension; history of stroke/ transient ischemic attack; history of myocardial infarction; and antiarrhythmic drugs, including β blockers and oral anticoagulation medications. HRVI indicates heart rate variability triangular index; MHR, mean heart rate; Ref., reference; RMSSD, square root of the mean squared differences of successive normal-to-normal intervals; and SDNN, standard deviation of the normal-to-normal intervals.

baseline rhythm (AF versus SR, *P* for interaction=0.52, Figures S1 and S2).

DISCUSSION

To the best of our knowledge, this is the largest study to have comprehensively investigated the prognostic power of HRV measures in a cohort of patients with AF. The main findings of our study are: (1) HRVI is an independent predictor of cardiovascular mortality in patients with AF; (2) HRVI also predicts all-cause mortality; and (3) HRVI correlates with various clinical parameters such as age, CHA_2DS_2-VASc score, and AF symptoms.

Heart Rate Variability Analysis in AF

The parameters of HRV are strong and independent predictors of mortality in patients with cardiovascular

Table 3. Associations of Heart Rate Variability Index With Secondary End Points

Outcome	No. of Events	Incidence/100 Patient-Years	Bivariable Model HR (95% CI)	*P* Value	Multivariable Model HR (95% CI)	*P* Value
All-cause mortality						
HRVI > median	63	1.28	Ref.		Ref.	
HRVI ≤ median	80	1.62	1.48 (1.06–2.06)	0.02	1.42 (1.02–1.98)	0.04
Myocardial infarction						
HRVI > median	22	0.45	Ref.		Ref.	
HRVI ≤ median	19	0.39	1.00 (0.54–1.85)	0.10	0.88 (0.47–1.64)	0.68
Ischemic stroke						
HRVI > median	21	0.43	Ref.		Ref.	
HRVI ≤ median	20	0.41	1.10 (0.60–2.04)	0.75	1.05 (0.56–1.94)	0.89
Any bleeding						
HRVI > median	147	3.23	Ref.		Ref.	
HRVI ≤ median	118	2.59	0.93 (0.73–1.18)	0.53	0.91 (0.72–1.12)	0.47
Hospitalization for heart failure						
HRVI > median	91	1.94	Ref.		Ref.	
HRVI ≤ median	86	1.83	1.08 (0.80–1.45)	0.62	1.02 (0.76–1.37)	0.90

Data are hazard ratios (HRs) (95% CIs). *P*-values were based on Cox proportional hazard models. Bivariable model was adjusted for age. Multivariable model was additionally adjusted for sex; body mass index; smoking status; history of diabetes mellitus; history of hypertension; history of stroke/ transient ischemic attack; history of myocardial infarction; and antiarrhythmic drugs, including β blockers and oral anticoagulation medications. HRVI indicates heart rate variability triangular index; and Ref., reference.

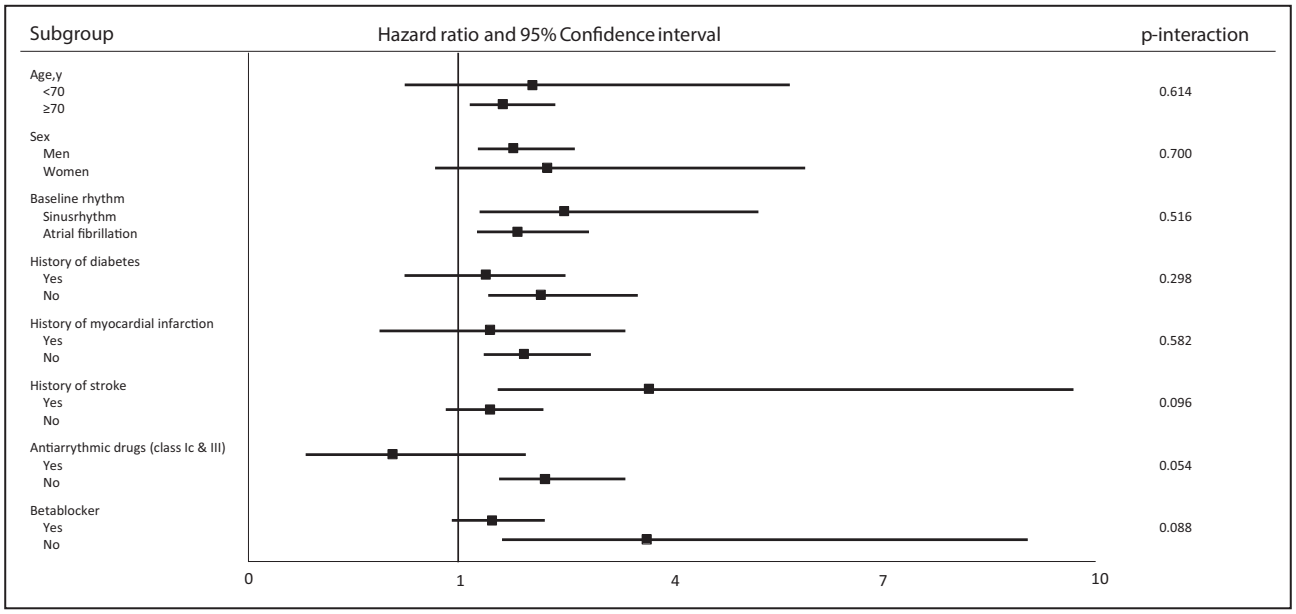

Figure 4. Estimated cardiovascular mortality hazard ratios of heart rate variability triangular index ≤ median (14.29) vs > median by different grouping variables.
The interaction tests whether the hazard ratio depends on the grouping variable; a small *P*-value supports that the effect of the heart rate variability triangular index differs between groups.

diseases who are in SR[6–19] as the sinus node is the "instantaneous writer" of cardiac autonomic function. However, in AF, sinus node activity is suppressed and can therefore not be used as a marker of HRV. Constant concealed activation of the AV node during AF results in irregularly irregular AV nodal conduction and hence to RR interval irregularity, which poses a challenge to HRV analysis. Only very few studies have investigated HRV analysis during AF. Five studies showed an association between depressed HRV, respectively depressed heart rate irregularity, and adverse outcome in patients with AF.[40–44] Stein et al assessed conventional time-domain measures of HRVI in 21 patients with AF suffering from severe mitral regurgitation.[41] Here, the reduction of the SD of the average NN interval calculated over 5 minutes was a significant predictor of the combined risk of mortality or requirement for mitral valve surgery in univariable analysis. Frey et al investigated HRV in 35 patients with AF suffering from CHF with reduced ejection fraction.[40] In this study, the SD of the average NN interval was the only independent parameter associated with survival on multivariable analysis. Yamada et al showed that even adjustment for cardiovascular comorbidities, entropy measures (Shannon entropy and approximate entropy) were significant predictors of cardiac death.[42] Finally, in a post hoc analysis of 155 AF patients with CHF included in the MUSIC (Muerte Subita en Insufficiencia Cardiaca) study, reduced approximate entropy, but not traditional HRV parameters (SD of the NN intervals, square root of the mean squared differences of successive NN intervals, the percentage of RR interval differences of successive NN intervals >50 ms = pNN50) predicted all-cause and sudden death.[43] In a post hoc analysis of 68 patients who had AF at inclusion in the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) study, Plantonov et al showed that after adjustment for significant clinical covariates, pNN20 <87%, but neither SD of the NN intervals, square root of the mean squared differences of successive NN intervals, nor approximate entropy, independently predicted mortality. To date, our study is by far the largest study that has assessed HRV in a cohort of patients with AF (n=1922). We were able for the first time to demonstrate that HRVI independently predicts cardiovascular mortality in patients with AF.

HRVI is a simple geometrical measure of HRV that can be derived from standard ECG recordings and expresses overall HRV.[17] Depressed HRVI reflects sympathovagal imbalance, but does not distinguish between particular changes in sympathetic and vagal activity.[45,46] Of note, other measures of HRV were not associated with mortality when adjusted for clinical covariates. This may be a result of the method of HRVI calculation, which is known to be robust and highly reproducible.[47] It overcomes the disadvantages of other HRV measures, as it is less affected by noise and artifacts.[48] For the calculation of HRVI, no difficult and time-consuming manual editing of the RR interval series is necessary. In contrast, methods based on SD of NN intervals require artifact-clear recognition of the ECG.[48]

In general, cut-offs of HRV parameters have not been clearly established.[37–39] Therefore, the classification of "abnormal" HRV remains difficult as it depends on the selection of patients, analysis methods, length of ECG recordings, and conditions in which HRV is assessed. This is one major reason why HRV analysis still has limited clinical use. According to the Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, albeit published more than 20 years ago,[37] an HRVI <15 is considered to be severely depressed, which is close to the median HRVI that we used in our cohort (ie, 14.29).

HRV Index as a Predictor of Outcome

The prognostic value of HRVI when assessed during SR has been investigated in various studies. Whereas both HRVI and left ventricular ejection fraction have been shown to perform equally well in predicting all-cause mortality in survivors of acute MI, HRVI was a better predictor of arrhythmic complications than left ventricular ejection fraction.[9] Furthermore, combining the left ventricular ejection fraction with HRVI improved specificity in predicting all-cause mortality. In another cohort of post-MI patients, low HRVI was shown to strongly predict arrhythmic events.[49] In patients with chronic CHF, a reduced HRVI was also found to be related to survival, independent of and of incremental value to left ventricular function.[11] Finally, even in the setting of coronary artery disease on chronic hemodialysis, a patient group with a high burden of comorbidity, decreased HRVI was a significant and independent predictor of cardiac death.[50] Therefore, though consistent with previous observations that reductions in HRVI are associated with adverse outcome, our findings show for the first time that HRVI is also associated with adverse outcomes in patients with AF. With regard to the results of subgroup analyses, the prognostic power of HRVI was not affected by baseline rhythm (SR versus AF). In addition, although β blockers and antiarrhythmic drugs have been described to alter HRV,[51,52] HRVI predicted cardiovascular mortality irrespective of the intake of β blockers or antiarrhythmics. Of note, the numerically highest risk of cardiovascular death was observed in patients who were in AF on baseline ECG and had an impaired HRVI.

Limitations

Several limitations have to be taken into account when interpreting our results. First, we assessed parameters of HRV in short-term ECG recordings over 5 minutes, whereas the majority of prior studies have assessed HRV during 24-hour Holter recordings.[6–11,13,14,17–19,40–42] However, our results indicate that HRV assessed from short-term recordings may be used for initial risk stratification of patients with AF. Nevertheless, it may be that HRV measured over longer periods may provide more prognostic information in patients with AF. Therefore, validation of our findings in 24-hour or 7-day Holter recordings is warranted. Second, the majority of patients were treated with drugs that may modify HRV. However, in subgroup analyses we observed no association of antiarrhythmics or β blockers with any HRV measure or prognosis. Third, this study is not able to establish causality of the potential mechanisms linking HRV and outcome in patients with AF. Therefore, the question whether decreased HRV is part of the pathophysiologic pathway leading to increased mortality in patients with AF or merely a marker of poor prognosis cannot be answered. Although the prognostic power of HRVI was independent of multiple clinical covariates, it cannot be excluded that reduced HRVI identified patients with unknown confounders with an impact on survival. Finally, this is a secondary, exploratory analysis from the Swiss-AF cohort and not the primary outcome.

Clinical Implications and Conclusions

Patients with AF are at high risk of serious cardiovascular events; therefore, establishing a new clinical tool for the identification of high-risk patients with AF is important. Our data indicate that HRVI measured in a single routine ambulatory 5-minute ECG-recording in AF patients is an independent predictor of cardiovascular mortality. This study suggests that analysis of the variability of the ventricular response in AF may also have prognostic implications when measured during AF. However, because of known limitations of HRV analysis during AF, where an increased background HRV is present, analysis of a RR interval time series in AF may have to be approached differently. Therefore, the development of new indices that focus on quantifying RR-interval irregularity instead of RR-interval variability might be promising for risk stratification in AF in the future.

ARTICLE INFORMATION

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Disclosures

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Supplementary Materials

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Data S1.

Supplemental Methods

Definition of study endpoints

Mortality

Deaths are categorized as either non-cardiovascular or cardiovascular. All deaths are assumed to be cardiovascular unless a non-cardiovascular cause can be clearly provided.

Cardiovascular death includes a broad spectrum of cardiac deaths, such as cardiogenic shock, arrhythmia/sudden death, cardiac rupture, stroke, pulmonary embolism, ruptured aortic aneurysm or dissection. Furthermore, all hemorrhagic deaths are classified as cardiovascular deaths.

Non-cardiovascular death requires a clear documentation of non-cardiac and nonvascular cause, for example respiratory failure (excluding cardiogenic pulmonary edema), neoplasm, infections/sepsis, and trauma (including suicide and homicide).

Myocardial infarction

A rise and/or fall of cardiac troponin with at least one value above the 99th percentile of the upper reference limit in a clinical setting consistent with myocardial infarction is required for the definition of myocardial infarction. Additionally, one of the following features is necessary: typical symptoms of ischaemia, new significant ST-T elevations and/or depressions, as well as left bundle-branch block on surface ECG, development of pathological Q waves on the ECG, imaging evidence of new regional wall motion abnormality or new loss of viable myocardium, identification of an intracoronary thrombus verified by angiography or autopsy.

Stroke

An acute focal neurological deficit of vascular origin consistent with imaging (computed tomography or cMRI) or autopsy is required for the definition of stroke. Stroke is classified as ischaemic, haemorrhagic or of unknown cause (based on imaging findings, or autopsy).TOAST classification is used for further differentiation of ischaemic stroke. Fatal stroke is defined as all-cause mortality within a timeframe of 30 days after stroke.

Bleeding

Bleedings are divided into two different categories:

1) We define **major bleeding** according to the criteria of the International Society on Thrombosis and Haemostasis, as overt bleedings with a fatal outcome, transfusion of at least two blood units, a drop in haemoglobin level of ≥20 g/l within 7 days, or symptomatic bleeding in a critical organ (intracranial, intraspinal, intraocular, intra-articular, pericardial, retroperitoneal, intramuscular with compartment syndromvereine).
2) **Clinically relevant non-major bleeding** is defined as a bleeding event that is clinically overt, and does not fulfill the criteria of a major bleeding event. These bleedings include:
   - hospital admission for bleeding or
   - a change in antithrombotic therapy or
   - physician guided medical or surgical treatment for bleeding.

Hospitalization for congestive heart failure

Hospitalization for acute heart failure is defined as: any hospitalization for acute heart failure that leads to at least one overnight stay. If it's not clear whether the reason for a patient's hospitalization is acute heart failure or not, this event/incidence should in doubt be classified as acute heart failure. The following clinical features could be used as an indication for heart failure: positive hepato-jugular reflux, rales and 3rd heart sound, leg swelling/leg edema and distension of the neck veins.

Table S1. Correlation between heart rate variability measures and clinical features.

	HRVI	SDNN	RMSSD	MHR
HRVI		-0.021	0.287†	-0.570†
SDNN	-0.021		0.566†	0.040
RMSSD	0.287†	0.566†		0.033
MHR	-0.570†	0.040	0.033	
Age	-0.066*	0.105†	0.173†	0.151†
Duration of AF	-0.035	-0.055*	-0.125†	-0.014
CHA_2DS_2-VASc score	-0.070†	0.067†	0.140†	0.142†
Systolic blood pressure	0.093†	-0.028	-0.010	-0.133†
Diastolic blood pressure	0.066†	-0.052*	0.032	-0.037
Body mass index	0.250	0.009	0.420	0.103†
AF symptoms[#]	-0.061*	-0.016	-0.038*	0.086†
Sex				
Male	14.7 (12.2-18.1)	96.8 (66.5-140.0)	42.7 (30.4-58.5)	108.1 (71.3-148.6)
Female	14.8 (12.3-18.5)	93.9 (59.1-143.8)	40.3 (29.1-55.2)	105.7 (73.1-147.5)

Data represent Spearman`s rank correlation coefficient or median and interquartile ranges. [#]According to EHRA classification. AF = atrial fibrillation. HRVI = heart rate variability triangular index. MHR = mean heart rate. RMSSD = square root of the mean squared differences of successive normal-to-normal intervals. SDNN = standard deviation of the normal-to-normal intervals. *p<0.05, † p<0.005

Figure S1. Prognostic impact of heart rate variability triangular index assessed during atrial fibrillation. Kaplan-Meier curves of cardiovascular mortality stratified by the median heart rate variability triangular index.

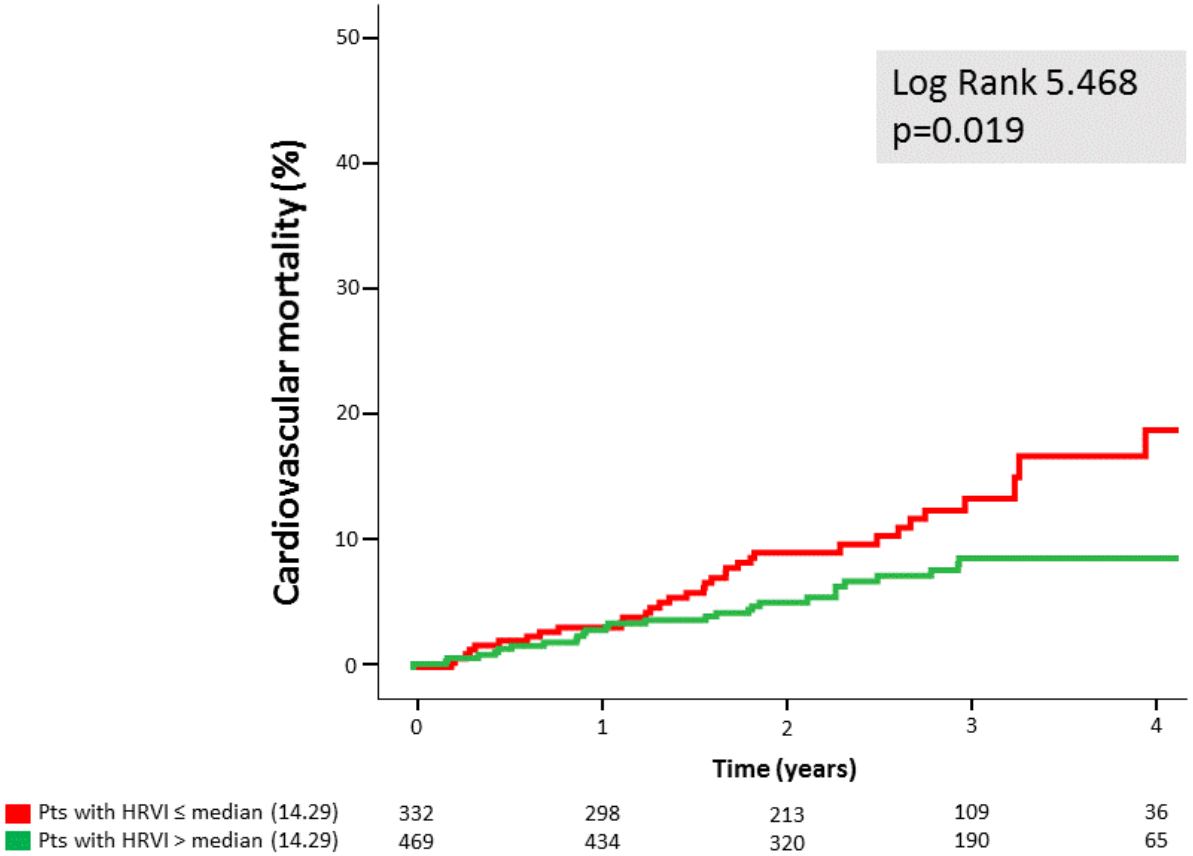

Figure S2. Prognostic impact of heart rate variability triangular index assessed during sinus rhythm. Kaplan-Meier curves of cardiovascular mortality stratified by the median heart rate variability triangular index.