




ORIGINAL RESEARCH

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

Peter Hämmerle, MD; Christian Eick, MD; Steffen Blum , MD, PhD; Vincent Schlageter, PhD; Axel Bauer, MD; Konstantinos D. Rizas, MD; Ceylan Eken, PhD; Michael Coslovsky, PhD; Stefanie Aeschbacher , PhD; Philipp Krisai , MD; Pascal Meyre, MD, PhD; Jean-Marc Vesin, PhD; Nicolas Rodondi, MD; Elisavet Moutzouri , MD; Jürg Beer , MD; Giorgio Moschovitis, MD; Richard Kobza , MD; Marcello Di Valentino, MD; Valentina D. A. Corino, PhD; Rita Laureanti , PhD; Luca Mainardi, PhD; Leo H. Bonati, MD; Christian Sticherling , MD; David Conen , MD; Stefan Osswald, MD; Michael Kühne , MD*; Christine S. Zuern , MD*; Swiss-AF Study Investigators[†]

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 \leq 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.

Correspondence to: Christine S. Zuern, MD, FESC, Department of Cardiology, Universitätsspital Basel, Petersgraben 4, CH-4031 Basel, Switzerland. E-mail: christine.meyerzuern@usb.ch

Supplementary Materials for this article are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.016075>

*Dr Kühne and Dr Zuern contributed equally to this work and are co-last authors.

[†]A complete list of the Swiss Atrial Fibrillation Cohort Study investigators can be found in the Supplemental Material.

For Sources of Funding and Disclosures, see page 9.

© 2020 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

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,

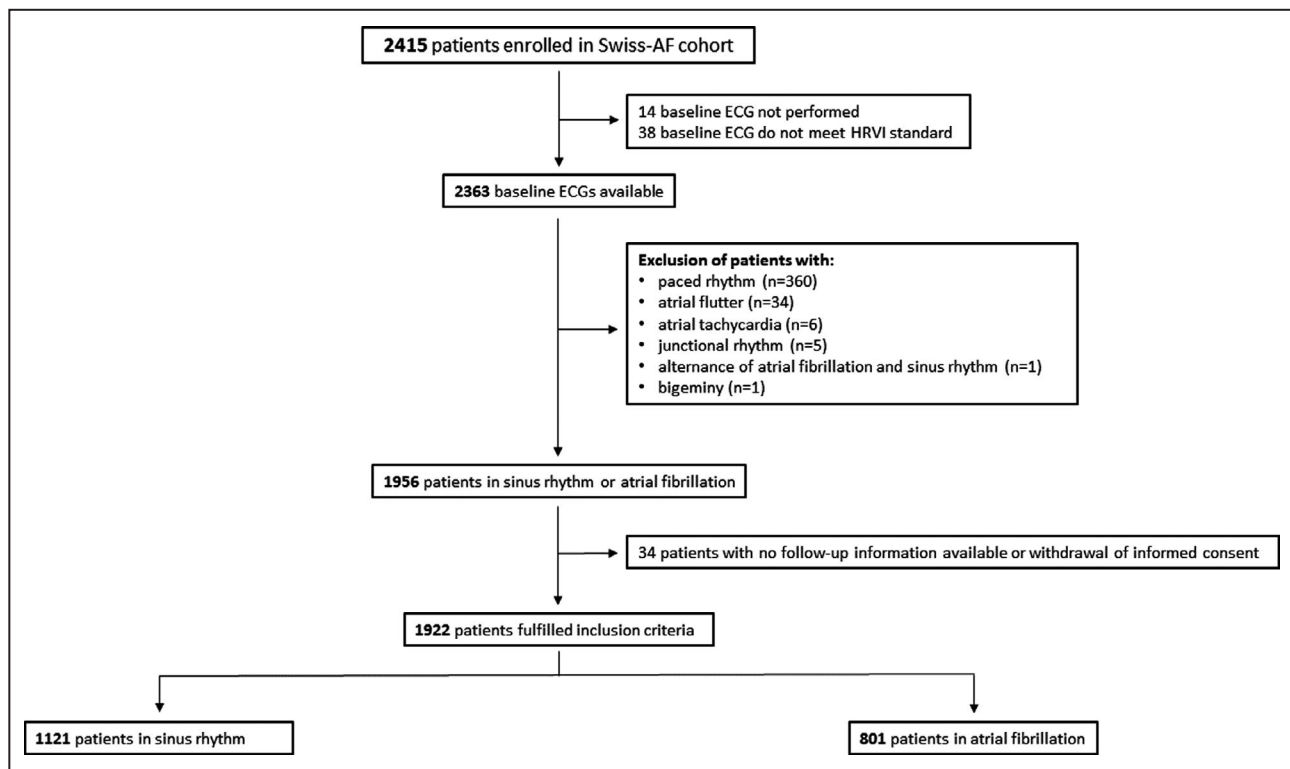


Figure 1. Flow chart of patient selection from the Swiss Atrial Fibrillation (Swiss-AF) Cohort Study. HRVI indicates heart rate variability triangular index.

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 μ V/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 software³⁷: 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 \pm SD and were analyzed using the *t* test. Categorical variables

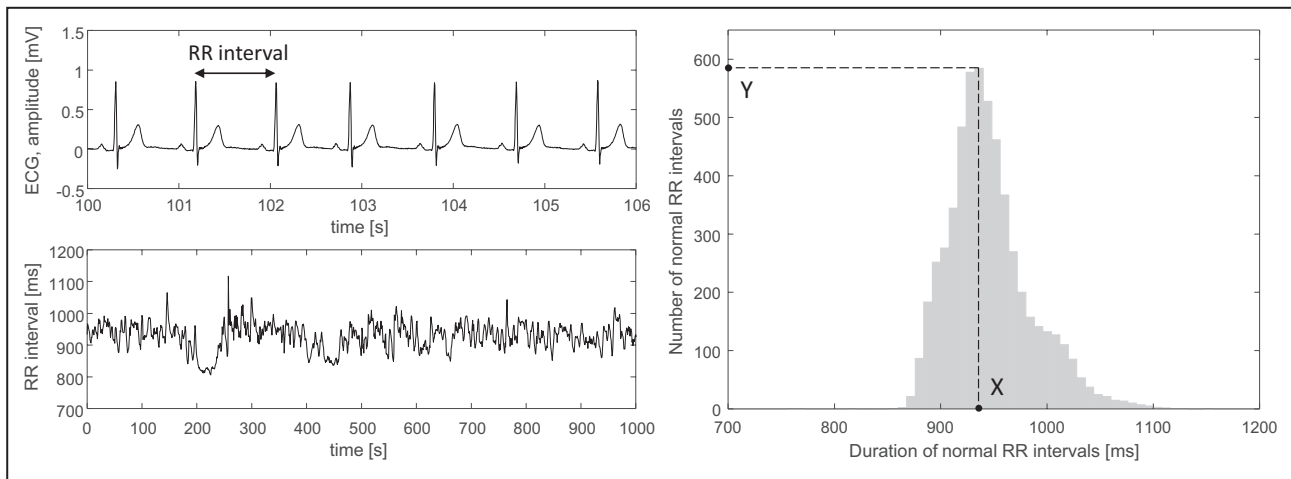


Figure 2. Calculation of heart rate variability triangular index (HRVI).

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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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, non-survivors 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 $\text{HRVI} \leq \text{median}$, 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 ₂ DS 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; CHA₂DS₂-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 I (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

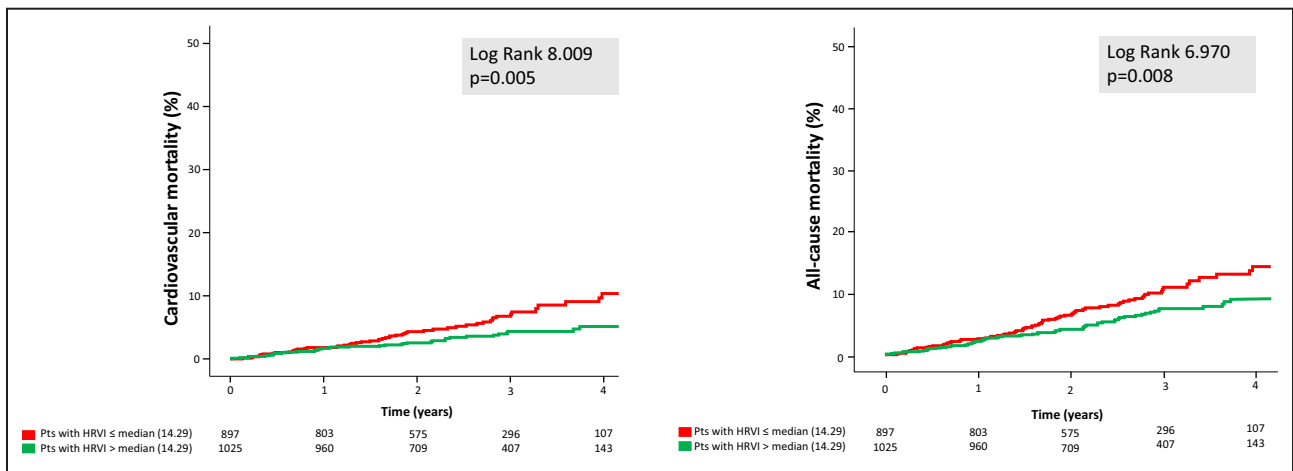


Figure 3. Prognostic impact of heart rate variability triangular index (HRVI) in the entire study cohort.

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 Patient 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, CHA₂DS₂-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.

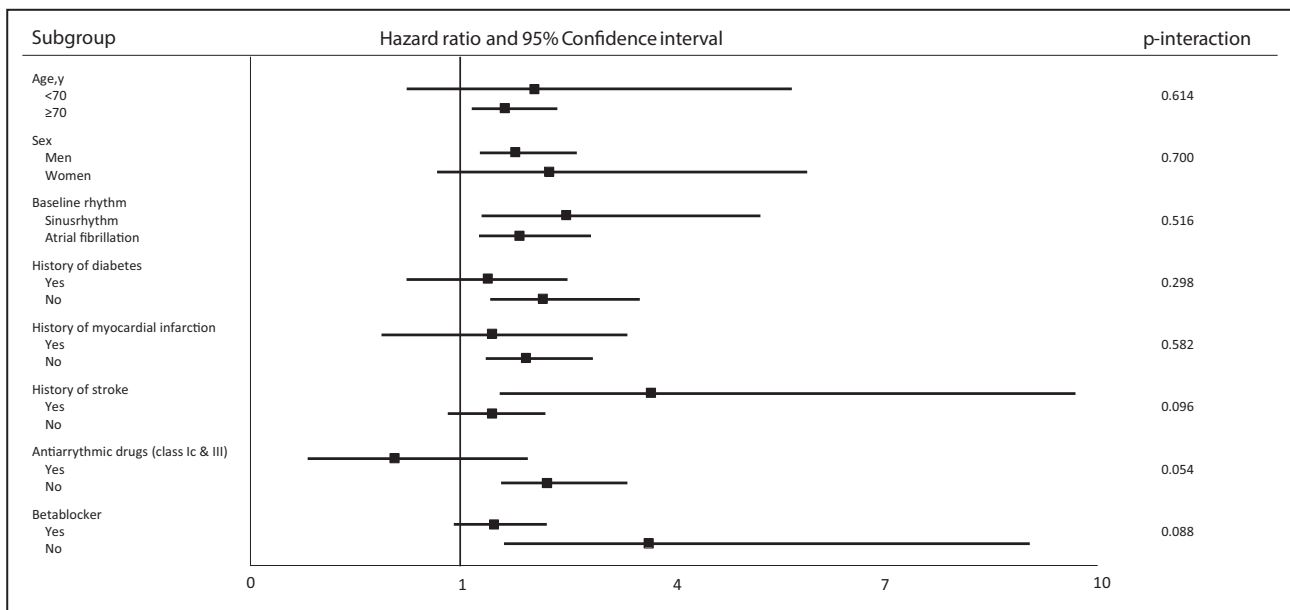


Figure 4. Estimated cardiovascular mortality hazard ratios of heart rate variability triangular index ≤ median (14.29) vs > median by different grouping variables.

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 SR⁶⁻¹⁹ 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 Insuficiencia 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

Received February 27, 2020; accepted June 19, 2020.

Affiliations

From the Department of Cardiology (P.H., S.B., S.A., P.K., P.M., C.S., S.O., M.K., C.S.Z.), and Cardiovascular Research Institute Basel (P.H., S.B., V.S., C.E., M.C., S.A., P.K., P.M., C.S., D.C., S.O., M.K., C.S.Z.), University Hospital Basel, Basel, Switzerland; Department of Cardiology, University Hospital Tübingen, Tübingen, Germany (C.E.); University Clinic of Internal Medicine III, Cardiology and Angiology, Medical University of Innsbruck, Austria (A.B.); Medizinische Klinik und Poliklinik, I Munich University Clinic, Munich, Germany (K.D.R.); German Center for Cardiovascular Research partner site, Munich Heart Alliance, Munich, Germany (K.D.R.); Swiss Federal Institute of Technology, Lausanne, Switzerland (J.-M.V.); Institute of Primary Health Care (BIHAM), University of Bern, Switzerland (N.R., E.M.); Department of General Internal Medicine, Inselspital Bern University Hospital, University of Bern, Switzerland (N.R., E.M.); Department of Medicine Cantonal Hospital of Baden and Molecular Cardiology, University Hospital of Zurich, Switzerland (J.B.); Department of Cardiology, EOC Ospedale Regionale di Lugano, Lugano, Switzerland (G.M.); Division of Cardiology, Luzerner Kantonsspital, Luzern, Switzerland

(R.K.); Department of Cardiology, EOC Ospedale San Giovanni, Bellinzona, Switzerland (M.D.V.); Biosignals, Bioimaging and Bioinformatics Laboratory (B3-Lab), Department of Electronics, Information and Bioengineering (DEIB), Politecnico di Milano, Milan, Italy (V.D.C., R.L., L.M.); Department of Neurology and Stroke Center, University Hospital Basel, University of Basel, Switzerland (L.H.B.); and Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Canada (D.C.).

Sources of Funding

The Swiss-AF study is supported by grants from the Swiss National Science Foundation (grant numbers 33CS30_1148474, 33CS30_177520, 32473B_176178), the Swiss Heart Foundation, the Foundation for Cardiovascular Research Basel (FCVR), and the University of Basel. Dr Conen holds a McMaster University Department of Medicine Mid-Career Research Award. His work is supported by the Hamilton Health Sciences RFA Strategic Initiative Program. Dr Bonati received grants from the Swiss National Science Foundation, the University of Basel (Basel, Switzerland), the Swiss Heart Foundation (Berne, Switzerland), and the "Stiftung zur Förderung der gastroenterologischen und allgemeinen klinischen Forschung sowie der medizinischen Bildauswertung" (Basel, Switzerland).

Disclosures

Dr Zuern reports a research grant from Medtronic and speaker fees from Vifor Pharma and Novartis. Dr Conen has received speaker fees from Servier, Canada. Dr Kühne has received grants from the Swiss National Science Foundation and the Swiss Heart Foundation, and lecture/consulting fees from Daiichi-Sankyo, Boehringer Ingelheim, Bayer, Pfizer-BMS, AstraZeneca, Sanofi-Aventis, Novartis, MSD, Medtronic, Boston Scientific, St. Jude Medical, Biotronik, Sorin, Zoll, and Biosense Webster. Dr Kobza received institutional grants from Abbott, Biosense-Webster, Biotronik, Boston-Scientific, Medtronic, and Sis-Medical. Dr Bonati has received an unrestricted research grant from AstraZeneca, and consultancy or advisory board fees or speaker's honoraria from Amgen, Bayer, Bristol-Myers Squibb, Claret Medical, and InnovHeart, and travel grants from AstraZeneca and Bayer. The remaining authors have no disclosures to report.

Supplementary Materials

Appendix S1

Data S1

Table S1

Figures S1–S2

REFERENCES

- Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110:1042–1046.
- Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34:2746–2751.
- Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946–952.
- Conen D, Chae CU, Glynn RJ, Tedrow UB, Everett BM, Buring JE, Albert CM. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. *JAMA*. 2011;305:2080–2087.
- Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. 2003;107:2920–2925.
- Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol*. 1987;59:256–262.
- La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet*. 1998;351:478–484.
- Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation*. 1992;85:164–171.
- Odemuyiwa O, Malik M, Farrell T, Bashir Y, Poloniecki J, Camm J. Comparison of the predictive characteristics of heart rate variability index and left ventricular ejection fraction for all-cause mortality, arrhythmic events and sudden death after acute myocardial infarction. *Am J Cardiol*. 1991;68:434–439.
- Martin GJ, Magid NM, Myers G, Barnett PS, Schaad JW, Weiss JS, Lesch M, Singer DH. Heart rate variability and sudden death secondary to coronary artery disease during ambulatory electrocardiographic monitoring. *Am J Cardiol*. 1987;60:86–89.
- Wijbenga JA, Balk AH, Meij SH, Simoons ML, Malik M. Heart rate variability index in congestive heart failure: relation to clinical variables and prognosis. *Eur Heart J*. 1998;19:1719–1724.
- Binder T, Frey B, Porenta G, Heinz G, Wutte M, Kreiner G, Gossinger H, Schmidinger H, Pacher R, Weber H. Prognostic value of heart rate variability in patients awaiting cardiac transplantation. *Pacing Clin Electrophysiol*. 1992;15:2215–2220.
- Brouwer J, van Veldhuisen DJ, Man in 't Veld AJ, Haaksma J, Dijk WA, Visser KR, Boomsma F, Dunselman PH. Prognostic value of heart rate variability during long-term follow-up in patients with mild to moderate heart failure. The Dutch Ibopamine Multicenter Trial Study Group. *J Am Coll Cardiol*. 1996;28:1183–1189.
- Ponikowski P, Anker SD, Chua TP, Szelemej R, Piepoli M, Adamopoulos S, Webb-Peploe K, Harrington D, Banasiak W, Wrabec K, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1997;79:1645–1650.
- Priori SG, Aliot E, Blomstrom-Lundqvist C, Bossaert L, Breithardt G, Brugada P, Camm AJ, Cappato R, Cobbe SM, Di Mario C, et al. Task Force on sudden cardiac death of the European Society of Cardiology. *Eur Heart J*. 2001;22:1374–1450.
- Schwartz PJ, La Rovere MT. ATRAMI: a mark in the quest for the prognostic value of autonomic markers. Autonomic Tone and Reflexes After Myocardial Infarction. *Eur Heart J*. 1998;19:1593–1595.
- Malik M, Farrell T, Cripps T, Camm AJ. Heart rate variability in relation to prognosis after myocardial infarction: selection of optimal processing techniques. *Eur Heart J*. 1989;10:1060–1074.
- Myers GA, Martin GJ, Magid NM, Barnett PS, Schaad JW, Weiss JS, Lesch M, Singer DH. Power spectral analysis of heart rate variability in sudden cardiac death: comparison to other methods. *IEEE Trans Biomed Eng*. 1986;33:1149–1156.
- Yi G, Goldman JH, Keeling PJ, Reardon M, McKenna WJ, Malik M. Heart rate variability in idiopathic dilated cardiomyopathy: relation to disease severity and prognosis. *Heart*. 1997;77:108–114.
- Schauerer P, Scherlag BJ, Pitha J, Scherlag MA, Reynolds D, Lazzara R, Jackman WM. Catheter ablation of cardiac autonomic nerves for prevention of vagal atrial fibrillation. *Circulation*. 2000;102:2774–2780.
- Bauer A, Deisenhofer I, Schneider R, Zrenner B, Barthel P, Karch M, Wagenpfeil S, Schmitt C, Schmidt G. Effects of circumferential or segmental pulmonary vein ablation for paroxysmal atrial fibrillation on cardiac autonomic function. *Heart Rhythm*. 2006;3:1428–1435.
- Horan LG, Kistler JC. Study of ventricular response in atrial fibrillation. *Circ Res*. 1961;9:305–311.
- Rawles JM, Rowland E. Is the pulse in atrial fibrillation irregularly irregular? *Br Heart J*. 1986;56:4–11.
- Billette J, Nadeau RA, Roberge F. Relation between the minimum RR interval during atrial fibrillation and the functional refractory period of the AV junction. *Cardiovasc Res*. 1974;8:347–351.
- Langendorf R, Pick A. Ventricular response in atrial fibrillation. Role of concealed conduction in the AV junction. *Circulation*. 1965;32:69–75.
- Moore EN. Observations on concealed conduction in atrial fibrillation. *Circ Res*. 1967;21:201–208.
- Vikman S, Lindgren K, Makikallio TH, Yli-Mayry S, Airaksinen KE, Huikuri HV. Heart rate turbulence after atrial premature beats before spontaneous onset of atrial fibrillation. *J Am Coll Cardiol*. 2005;45:278–284.
- Jons C, Raatikainen P, Gang UJ, Huikuri HV, Joergensen RM, Johannesen A, Diken U, Messier M, McNitt S, Thomsen PE. Autonomic dysfunction and new-onset atrial fibrillation in patients with left ventricular systolic dysfunction after acute myocardial infarction: a CARISMA substudy. *J Cardiovasc Electrophysiol*. 2010;21:983–990.

29. Patterson E, Po SS, Scherlag BJ, Lazzara R. Triggered firing in pulmonary veins initiated by in vitro autonomic nerve stimulation. *Heart Rhythm*. 2005;2:624–631.
30. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. *Circulation*. 2002;105:2753–2759.
31. Shen MJ, Choi EK, Tan AY, Lin SF, Fishbein MC, Chen LS, Chen PS. Neural mechanisms of atrial arrhythmias. *Nat Rev Cardiol*. 2011;9:30–39.
32. Yamazaki M, Vaquero LM, Hou L, Campbell K, Zlochiver S, Klos M, Mironov S, Berenfeld O, Honjo H, Kodama I, et al. Mechanisms of stretch-induced atrial fibrillation in the presence and the absence of adrenergic stimulation: interplay between rotors and focal discharges. *Heart Rhythm*. 2009;6:1009–1017.
33. Agarwal SK, Norby FL, Whitsel EA, Soliman EZ, Chen LY, Loehr LR, Fuster V, Heiss G, Coresh J, Alonso A. Cardiac autonomic dysfunction and incidence of atrial fibrillation: results from 20 years follow-up. *J Am Coll Cardiol*. 2017;69:291–299.
34. Nortamo S, Ukkola O, Kiviniemi A, Tulppo M, Huikuri H, Perkiomaki JS. Impaired cardiac autonomic regulation and long-term risk of atrial fibrillation in patients with coronary artery disease. *Heart Rhythm*. 2018;15:334–340.
35. Perkiomaki J, Ukkola O, Kiviniemi A, Tulppo M, Ylitalo A, Kesaniemi YA, Huikuri H. Heart rate variability findings as a predictor of atrial fibrillation in middle-aged population. *J Cardiovasc Electrophysiol*. 2014;25:719–724.
36. Conen D, Rodondi N, Mueller A, Beer J, Auricchio A, Ammann P, Hayoz D, Kobza R, Moschovitis G, Shah D, et al. Design of the Swiss Atrial Fibrillation Cohort Study (Swiss-AF): structural brain damage and cognitive decline among patients with atrial fibrillation. *Swiss Med Wkly*. 2017;147:w14467.
37. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation*. 1996;93:1043–1065.
38. Nunan D, Sandercock GR, Brodie DA. A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. *Pacing Clin Electrophysiol*. 2010;33:1407–1417.
39. Dantas EM, Kemp AH, Andreao RV, da Silva VJD, Brunoni AR, Hoshi RA, Bensenor IM, Lotufo PA, Ribeiro ALP, Mill JG. Reference values for short-term resting-state heart rate variability in healthy adults: results from the Brazilian Longitudinal Study of Adult Health-ELSA-Brasil study. *Psychophysiology*. 2018;55:e13052.
40. Frey B, Heinz G, Binder T, Wutte M, Schneider B, Schmidinger H, Weber H, Pacher R. Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart failure. *Am Heart J*. 1995;129:58–65.
41. Stein KM, Borer JS, Hochreiter C, Devereux RB, Kligfield P. Variability of the ventricular response in atrial fibrillation and prognosis in chronic nonischemic mitral regurgitation. *Am J Cardiol*. 1994;74:906–911.
42. Yamada A, Hayano J, Sakata S, Okada A, Mukai S, Ohte N, Kimura G. Reduced ventricular response irregularity is associated with increased mortality in patients with chronic atrial fibrillation. *Circulation*. 2000;102:300–306.
43. Cygankiewicz I, Corino V, Vazquez R, Bayes-Genis A, Mainardi L, Zareba W, de Luna AB, Platonov PG; Investigators MT. Reduced irregularity of ventricular response during atrial fibrillation and long-term outcome in patients with heart failure. *Am J Cardiol*. 2015;116:1071–1075.
44. Platonov PG, Holmqvist F. Atrial fibrillatory rate and irregularity of ventricular response as predictors of clinical outcome in patients with atrial fibrillation. *J Electrocardiol*. 2011;44:673–677.
45. Billman GE, Schwartz PJ, Stone HL. Baroreceptor reflex control of heart rate: a predictor of sudden cardiac death. *Circulation*. 1982;66:874–880.
46. Schwartz PJ, Vanoli E, Stramba-Badiale M, De Ferrari GM, Billman GE, Foreman RD. Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. *Circulation*. 1988;78:969–979.
47. Ziegler D, Piolot R, Strassburger K, Lambeck H, Dannehl K. Normal ranges and reproducibility of statistical, geometric, frequency domain, and non-linear measures of 24-hour heart rate variability. *Horm Metab Res*. 1999;31:672–679.
48. Malik M, Farrell T, Camm AJ. Circadian rhythm of heart rate variability after acute myocardial infarction and its influence on the prognostic value of heart rate variability. *Am J Cardiol*. 1990;66:1049–1054.
49. Farrell TG, Bashir Y, Cripps T, Malik M, Poloniecki J, Bennett ED, Ward DE, Camm AJ. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. *J Am Coll Cardiol*. 1991;18:687–697.
50. Fukuta H, Hayano J, Ishihara S, Sakata S, Ohte N, Takahashi H, Yokoyama M, Toriyama T, Kawahara H, Yajima K, et al. Prognostic value of nonlinear heart rate dynamics in hemodialysis patients with coronary artery disease. *Kidney Int*. 2003;64:641–648.
51. Bigger JT Jr, Rolnitzky LM, Steinman RC, Fleiss JL. Predicting mortality after myocardial infarction from the response of RR variability to antiarrhythmic drug therapy. *J Am Coll Cardiol*. 1994;23:733–740.
52. Zuanetti G, Latini R, Neilson JM, Schwartz PJ, Ewing DJ. Heart rate variability in patients with ventricular arrhythmias: effect of antiarrhythmic drugs. Antiarrhythmic Drug Evaluation Group (ADEG). *J Am Coll Cardiol*. 1991;17:604–612.

SUPPLEMENTAL MATERIAL

Swiss-AF investigators*

University Hospital Basel and Basel University: Stefanie Aeschbacher, Chloe Auberson, Steffen Blum, Leo Bonati, Selinda Ceylan, David Conen, Simone Doerpfeld, Marc Girod, Peter Hämmerle, Philipp Krisai, Michael Kühne, Christine Meyer-Zürn, Pascal Meyre, Andreas U. Monsch, Christian Müller, Stefan Osswald, , Philipp Reddiess, Javier Ruperti Repilado, , Anne Springer, Fabienne Steiner, Christian Sticherling, Thomas Szucs, Gian Voellmin, Leon Zwimpfer. Principal Investigator: Stefan Osswald; Local Principal Investigator: Michael Kühne

University Hospital Bern: Faculty: Drahomir Aujesky, Urs Fischer, Juerg Fuhrer, Laurent Roten, Simon Jung, Heinrich Mattle; Research fellows: Luise Adam, Carole Elodie Aubert, Martin Feller, Claudio Schneider, Axel Loewe, Elisavet Moutzouri; Study nurses: Tanja Flückiger, Cindy Groen, Damiana Rakovic, Rylana Wenger, Lukas Ehram, Alexandra Nuoffer, Nathalie Schwab. Local Principal Investigator: Nicolas Rodondi

Stadtspital Triemli Zurich: Christopher Beynon, Roger Dillier, Michèle Deubelbeiss, Franz Eberli, Christine Franzini, Isabel Juchli, Claudia Liedtke, Jacqueline Nadler, Thayze Obst, Noreen Tynan, Xiaoye Schneider, Katrin Studerus, Dominik Weishaupt. Local Principal Investigator: Andreas Müller

Kantonsspital Baden: Simone Fontana, Silke Kuest, Karin Scheuch, Denise Hischier, Nicole Bonetti, Alexandra Grau, Jonas Villinger, Eva Laube, Philipp Baumgartner, Mark Filipovic, Marcel Frick, Giulia Montrasio, Stefanie Leuenberger, Franziska Rutz. Local Principal Investigator: Jürg-Hans Beer

Cardiocentro Lugano: Angelo Auricchio, Adriana Anesini, Cristina Camporini, Giulio Conte, Maria Luce Caputo, Francois Regoli. Local Principal Investigator: Tiziano Moccetti

Kantonsspital St. Gallen: Roman Brenner, David Altmann, Michaela Gemperle. Local Principal Investigator: Peter Ammann

Hôpital Cantonal Fribourg: Mathieu Firmann, Sandrine Foucras. Local Principal Investigator: Daniel Hayoz

Luzerner Kantonsspital: Benjamin Berte, Virginia Justi, Frauke Kellner-Weldon, Brigitta Mehmann, ,
Myriam Roth, Andrea Ruckli-Kaeppeli, Ian Russi, Kai Schmidt, Mabelle Young, Melanie Zbinden.
Local Principal Investigator: Richard Kobza

Ente Ospedaliero Cantonale Lugano: Jane Frangi-Kultalahti, Anica Pin, Luisa Vicari Local Principal
Investigator: Giorgio Moschovitis

University Hospital Geneva: Georg Ehret, Hervé Gallet, Elise Guillermet, Francois Lazeyras, Karl-Olof
Lovblad, Patrick Perret, Philippe Tavel, Cheryl Teres. Local Principal Investigator: Dipen Shah

University Hospital Lausanne: Nathalie Lauriers, Marie Méan, Sandrine Salzmann. Local Principal
Investigator: Jürg Schläpfer

Bürgerspital Solothurn: Andrea Grêt, Jan Novak, Sandra Vitelli. Local Principal Investigator: Frank-
Peter Stephan

Ente Ospedaliero Cantonale Bellinzona: Jane Frangi-Kultalahti, Augusto Gallino. Local Principal
Investigator: Marcello Di Valentino

University of Zurich/University Hospital Zurich: Fabienne Witassek, Matthias Schwenkglenks.

Medical Image Analysis Center AG Basel: Jens Würfel (Head), Anna Altermatt, Michael Amann, Petra
Huber, Esther Ruberte, Tim Sinnecker, Vanessa Zuber.

Clinical Trial Unit Basel: Michael Coslovsky (Head), Pascal Benkert, Gilles Dutilh, Milica Markovic,
Patrick Simon

Schiller AG Baar: Ramun Schmid

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 ₂ DS 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.

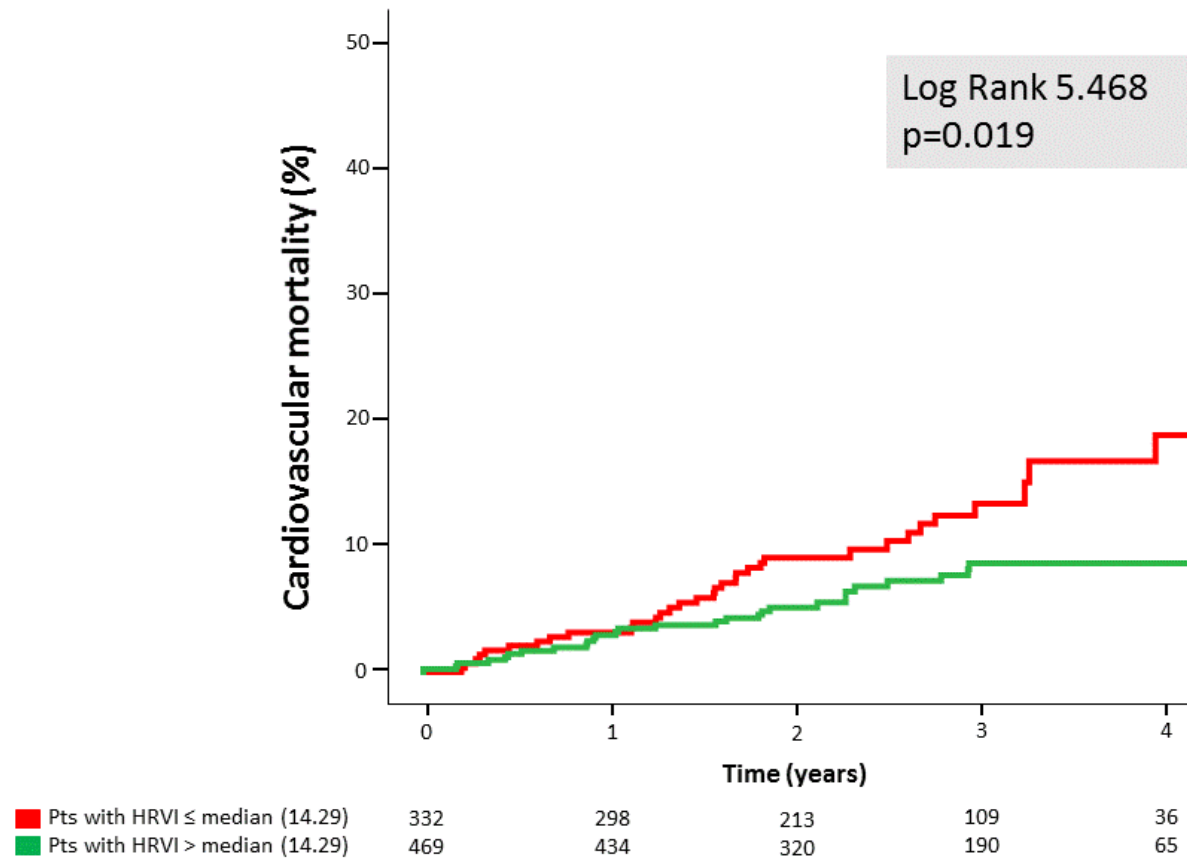


Figure S2. Prognostic impact of heart rate variability triangular index assessed during sinus rhythm. Kaplan-Meier curves of cardiovascular mortality stratified by the median heart rate variability triangular index.

