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CLINICAL RESEARCH

Ventricular rate in atrial fibrillation and the risk of heart failure and death

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Aims While clinical trials have suggested that a high ventricular rate is associated with increased risk of heart failure (HF) and mortality, all-comers studies are warranted.

Objective To assess 1-year risk of new-onset diagnosed HF and all-cause mortality among rate-control treated patients presenting with atrial fibrillation (AF) on an electrocardiogram (ECG) according to ventricular rate.

Methods and results ECGs recorded at the Copenhagen General Practitioners Laboratory (2001–15) were used to identify patients with AF. Multivariate Cox proportional hazard regression models were used to compare risk of new-onset HF and all-cause mortality after first ECG presenting with AF according to ventricular rate on ECG [<60, 60–79, 80–99, and 100–110, > 110 beats per minute (bpm)]. We identified 7408 patients in treatment with rate control drugs at time of first ECG presenting with AF [median age 78 years (Q1,Q3 = 70–85 years)], 45.8% male, median ventricular rate 83 bpm, (Q1,Q3 = 71–101 bpm)]. During 1-year follow-up, 666 (9.0%) of all patients with AF developed HF and 858 (11.6%) died. Patients with AF ventricular rates 100–110 bpm and >110 bpm had a hazard ratio (HR) of 1.46 (CI: 1.10–1.95) and 2.41 (CI: 1.94–3.00) respectively for new-onset HF, compared with 60–79 bpm. Similarly, patients with AF ventricular rates 100–110 bpm and >110 bpm had a HR of 1.44 (CI: 1.13–1.82) and 1.34 (CI: 1.08–1.65) respectively for all-cause mortality, compared with 60–79 bpm.

Conclusions Ventricular rates ≥100 bpm among patients presenting with AF on ECG in treatment with rate control drugs were associated with greater risk of both new-onset HF and all-cause mortality.

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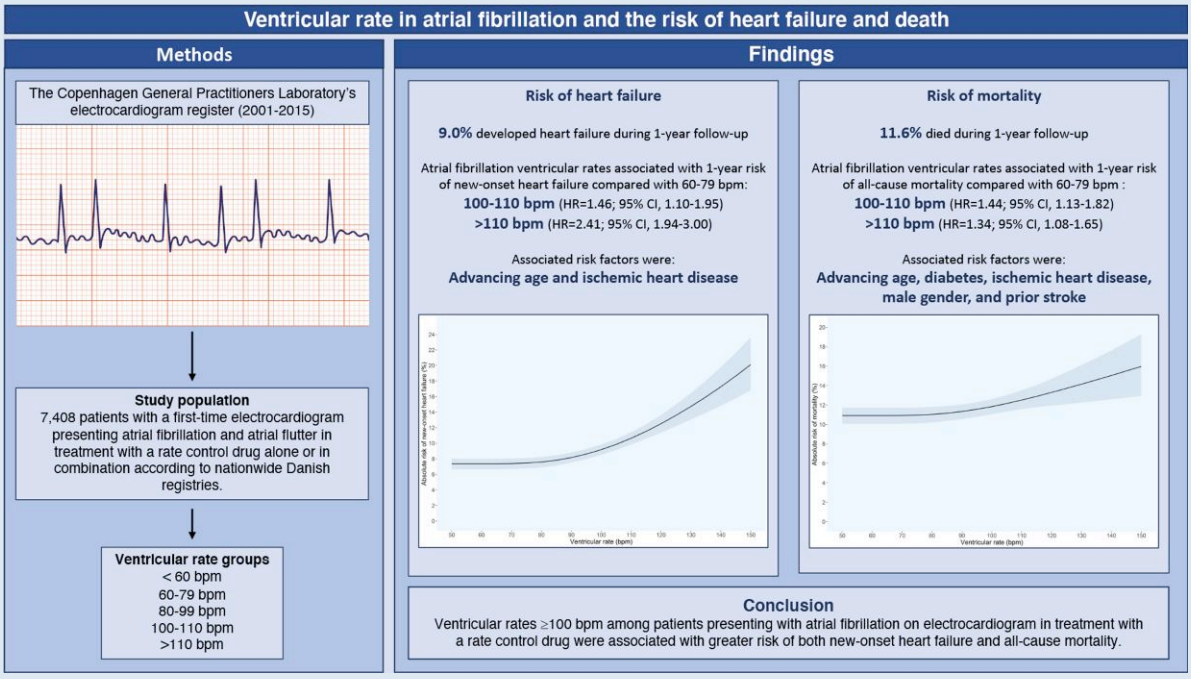
Graphical Abstract



Keywords Atrial fibrillation • Atrial flutter • Rate-control • Heart failure • Mortality

What's new?

- Among patients presenting with atrial fibrillation on an electrocardiogram in treatment with rate control drugs, ventricular rates ≥100 bpm were associated with greater risk of new-onset heart failure in a dose-response manner (i.e. higher ventricular rate was associated with greater HF risk).
- In addition, ventricular rates ≥100 among patients presenting with atrial fibrillation on an electrocardiogram in treatment with rate control drugs were likewise associated with a greater risk of 1-year mortality.
- The findings of the present study, although based on observational data, suggest that a lenient rate control approach aimed lower than recommended by current guidelines is associated with better outcomes.

Introduction

While rate-control and rhythm-control strategies, which both are considered important pillars of atrial fibrillation (AF) care, have all been associated with improved AF related symptoms, neither strategy has been conclusively shown to be superior in terms of improved survival and, thus, they are considered equal.[1,2] For example, the Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient vs. Strict Rate Control II (RACE II) trial showed that a lenient rate-control treatment strategy (<110 bpm) was non-inferior compared with a strict rate-control treatment strategy (<80 bpm) with regards to reducing AF symptoms and risk of mortality.[3] Furthermore, an analysis with pooled data from The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and Rate Control vs. Electrical cardioversion for persistent atrial fibrillation (RACE) trial comparing patients assigned to rate control also found no difference in major clinical events among patients assigned to strict rate-control strategy (≤80 bpm, AFFIRM trial) and lenient rate-control (<100 bpm, RACE trial).[4] However, the analysis found that patients with AF heart rates within study criteria of the two studies had better outcomes compared to patients with AF heart rates ≥100 bpm. Thus, lenient rate-control (<110 bpm) is a class II recommendation for management of asymptomatic patients with AF and to this day, identifying the most optimal rate-control treatment strategy for AF is still topics of investigation.[1,5] However, despite the positive findings on a lenient rate-control treatment approach in terms of survival in randomized clinical trials, higher resting ventricular rates have previously been associated with risk of tachycardia induced cardiomyopathy that may lead to increased risk of mortality.[6,7]

Therefore, to address these gaps in current knowledge, we used the Copenhagen General Practitioners Laboratory ECG register coupled with nationwide Danish registries, to identify 1-year risk of new-onset heart failure (HF) and all-cause mortality according to ventricular rate among all-comer patients presenting with AF on an ECG and in treatment with rate control drugs. Here, our hypothesis was that patients with dysregulated AF, may present with worse outcomes in an all-comer population presenting with AF on an ECG. Moreover, we aimed to identify factors associated with new-onset HF and mortality.

Methods

Data registries

In Denmark, all residents are given a personal identification number at date of birth or immigration through the Civil Registration System which allows cross-linkage of nationwide registries on an individual level.[8] The Danish register of Medicinal Product Statistics holds complete and detailed information on all dispensed drug prescriptions from Danish pharmacies since

1995 according to the Anatomical Therapeutic Chemical System.[9] All Danish pharmacies are by law obliged to register every dispensed prescription because of the partial reimbursement of drug expenses by the government financed healthcare system which makes the register both accurate and valid.[9] The National Patient Register holds information regarding every hospital admission and discharge since 1978 with one primary diagnosis and two or more diagnoses, which are recorded according to The International Classification of Diseases [diagnoses up until 1994 were recorded according to the 8th revision (ICD-8) and after according to the 10th revision (ICD-10)]. Surgical procedures are recorded according to the Nordic Medical Statistics Committees Classification of Surgical Procedures.[10] The Danish Register of Causes of Death holds information regarding date of death and primary cause of death which includes cardiovascular specific cause of death.[11] For additional information, see the supplementary appendix.

Electrocardiograms

In the greater region of Copenhagen, which covers ∼1.8 million residents, most patients are referred to The Copenhagen General Practitioners' Laboratory, or one of its satellite clinics, by their general practitioner for clinical tests including biochemical tests and recording of electrocardiograms (ECGs). At the Copenhagen General Practitioners' Laboratory, ECGs are recorded according to a standardized protocol and MUSE® Cardiology Information System (GE Healthcare, Wauwatosa, WI, USA) is used to store all digitally recorded ECGs. ECGs are later analysed using the latest version 23 of the Marquette 12SL algorithm. The Marquette AF determining algorithm has a sensitivity and specificity of 87.5% and 99.4%, respectively.[12]

Study cohort

Patients with a first-time ECG presenting with AF or atrial flutter from 2001–15 were identified using the Copenhagen General Practitioners' Laboratory ECG register. For inclusion, patients were required to be in treatment with a rate control drug alone or in combination (i.e. beta-blockers, digoxin, diltiazem, and verapamil) according to the Danish National Prescription Register within 180 days prior to date of first ECG presenting with AF. Date of first ECG presenting with AF was defined as date of inclusion (i.e. index). Patients were excluded if they had a prior history of HF, valvular heart surgery, pacemaker implantation, age <18 years, and age >100 years. Moreover, to increase the likelihood that the presenting ECG was the diagnostic ECG of AF, patients were excluded if they had a prescription of antiarrhythmic drugs (i.e. amiodarone, class I antiarrhythmics, and class III antiarrhythmics) within 180 days of ECG. All included patients were eligible for at least one year of follow-up.

Concomitant pharmacotherapy and comorbidity

Concomitant pharmacotherapy was defined as dispensed prescription within 180 days prior to index according to The National Prescription Register. Diabetes was defined as dispensed drug prescription of antidiabetic medication within 180 days before index or hospital admission or discharge with diabetes up to 10 years before index. Hypertension was identified from treatment with at least two claimed antihypertensive drug prescriptions 180 days before index, as done previously.[13] All other comorbidities were identified according to hospital admission discharge diagnoses up to 10 years before index according to The National Patient Register and these were bleeding, cancer, chronic obstructive pulmonary disease, diabetes, hyperthyroidism, ischaemic heart disease (IHD), kidney disease, and prior stroke. Moreover, previous cardiac surgery and hospital admissions with AF prior to index were also identified using The National Patient Register. For details, see the Supplementary material online, *Table S1*.

Study outcomes

The main study outcomes were 1-year risk of new-onset HF (i.e. a heart failure diagnosis in an in-hospital or and outpatient setting, whichever came first) and risk of all-cause mortality at 1-year follow-up after first ECG presenting with AF.

Statistical analyses

Continuous variables were presented as medians with interquartile ranges (IQR). Differences between continuous variables were compared using the Kruskal–Wallis test. Categorical variables were presented as numbers with percentages, and differences compared using Cochran–Armitage test for trend.

We grouped the ventricular rate: < 60, 60–79, 80–99, 100–110, and >110 bpm. A ventricular rate between 60 and 79 bpm was used as the comparative reference to mimic a strict rate-control group.[3] Cox proportional hazard regression models were used to compare risk of new-onset HF or all-cause mortality according to ventricular rate on ECG. Included in the models were variables that were considered clinically relevant including ventricular rate groups, sex, age (5-year increments), year of inclusion, kidney disease, diabetes, hypertension, IHD, stroke, concomitant pharmacotherapy with beta-blockers, verapamil or diltiazem, digoxin, renin angiotensin system inhibitors, statins, and anticoagulants (i.e. vitamin k antagonists and direct oral anticoagulants). We reported hazard ratios (HRs) with 95% confidence intervals (CI). Patients were followed up to one year from index or until date of emigration, passing the end of the observational period (31 December 2016), date of death, or admission to a Hospital with HF, whichever came first. Using cox regression models, we calculated 1-year absolute risks of new-onset HF and all-cause mortality according to ventricular rate group standardized to the distribution of clinically relevant variables.[14] We reported standardized absolute risks and 1-year standardized absolute risk differences with 95% CIs. Furthermore, we performed an additional landmark analysis for one-year mortality starting from second year after date of ECG recording. We also performed similar analyses according to type rate control drugs (i.e. beta-blockers, digoxin, verapamil or diltiazem, and ≥2 rate control drugs). Included in the model were sex, age (5-year increments), year of inclusion, kidney disease, diabetes, hypertension, IHD, stroke, renin angiotensin system inhibitors, statins, and anticoagulants (i.e. vitamin k antagonists and direct oral anticoagulants). For these analyses, beta-blocker treatment was used as the comparative reference.

For visualising the association between continuous ventricular rate and risk of new-onset HF and all-cause mortality adjusted for clinically clinical variables, we used restricted cubic splines with three knots according to the 0.10, 0.50, and 0.90 quantiles (i.e. 61, 83, and 123 bpm).

To test the robustness of our findings, we also performed several sensitivity analyses. First, we excluded patients with IHD to ensure that our results were not driven by a special subgroup of patients with IHD (e.g. beta-blockers are commonly used among patients with ischaemic cardiomyopathies). Second, while we excluded patients with known HF for the main analysis, we also excluded patients in pharmacological treatment with drugs commonly used to treat HF before index (i.e. renin angiotensin system inhibitors, loop-diuretics, and spironolactone) to increase likelihood of new-onset as opposed to undiagnosed HF. Third, we excluded patients with prior hospital admission with hyperthyroidism since it also can lead to AF and tachycardia. Fourth, we exclude patients with atrial flutter to ensure that our results were not driven by a special subgroup of patients (e.g. AF and atrial flutter have different pathophysiology and patient groups are different). Fifth, we assessed 3-year risk of study outcomes. For details, see the supplementary appendix.

For all analyses, a two-sided P <0.05 was considered to be statistically significant. Data management and analysis was performed using SAS, version 9.4 (SAS Institute, Cary, NC) and R version 4.2 [R Core Team (2020). R a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.r-project.org/].

Ethics

Register-based analyses, using de-identifiable data, are exempt from ethical approval in Denmark. The present study was registered with the Danish Data Protection Agency (*P*-2019-533). Danish law prohibits reporting of group numbers $n < 4$ and these were replaced with '<4' throughout the paper. The exact numbers are known to the investigators.

Results

Study cohort

We identified 7408 patients presenting with AF on an ECG with a median age of 78 years (IQR = 70–85 years), 45.8% were male, and the

Table 1 Characteristics for patients presenting with atrial fibrillation on electrocardiogram stratified by ventricular rate

	<60 bpm (*n* = 646)	60–79 bpm (*n* = 2492)	80–99 bpm (*n* = 2330)	100–110 bpm (*n* = 685)	>110 bpm (*n* = 1255)	Total (*n* = 7408)	*P*-value
Sex (male)	350 (54.2)	1161 (46.6)	1059 (45.5)	308 (45.0)	517 (41.2)	3395 (45.8)	<0.0001
Age, years (median)	81 [75, 87]	79 [72, 85]	78 [70, 85]	77 [69, 84]	75 [67, 82]	78 [70, 85]	<0.0001
Atrial fibrillation	595 (92.1)	2296 (92.1)	2133 (91.5)	605 (88.3)	1015 (80.9)	6644 (89.7)	<0.0001
Atrial flutter	51 (7.9)	196 (7.9)	197 (8.5)	80 (11.7)	240 (19.1)	764 (10.3)	<0.0001
Prior AF hospitalization	389 (60.2)	1661 (66.7)	1426 (61.2)	344 (50.2)	453 (36.1)	4273 (57.7)	<0.0001
Time to ECG recording, among patients with prior AF hospitalization, years (median)	5.2 [2.7, 9.9]	4.2 [1.8, 8.1]	3.5 [1.3, 7.7]	3 [1.1, 7.1]	2.8 [0.9, 6.2]	11.2 [3.1, 41.0]	<0.0001
Ventricular rate, bpm (median)	54 [50, 57]	71 [66, 75]	88 [84, 93]	105 [102, 107]	127 [118, 139]	83 [71, 101]	<0.0001
Rate control pharmacotherapy							
Beta-blockers	171 (26.5)	832 (33.4)	905 (38.8)	324 (47.3)	661 (52.7)	2893 (39.1)	<0.0001
Calcium channel blockers	59 (9.1)	160 (6.4)	231 (9.9)	87 (12.7)	125 (10.0)	662 (8.9)	0.0002
Digoxin	223 (34.5)	735 (29.5)	620 (26.6)	159 (23.2)	295 (23.5)	2032 (27.4)	<0.0001
≥2 rate control drugs	193 (29.9)	765 (30.7)	574 (24.6)	115 (16.8)	174 (13.9)	1821 (24.6)	<0.0001
Concurrent pharmacotherapy							
Acetylsalicylic acid	272 (42.1)	952 (38.2)	909 (39.0)	275 (40.1)	443 (35.3)	2851 (38.5)	0.03
Class II calcium channel blockers	131 (20.3)	408 (16.4)	402 (17.3)	90 (13.1)	227 (18.1)	1258 (17.0)	0.5
Diuretics	449 (69.5)	1782 (71.5)	1648 (70.7)	502 (73.3)	960 (76.5)	5341 (72.1)	0.0003
Loop diuretics	233 (36.1)	692 (27.8)	582 (25.0)	172 (25.1)	258 (20.6)	1937 (26.1)	<0.0001
Renin angiotensin system inhibitors	239 (37.0)	894 (35.9)	794 (34.1)	246 (35.9)	463 (36.9)	2636 (35.6)	0.8
Statins	161 (24.9)	571 (22.9)	537 (23.0)	141 (20.6)	287 (22.9)	1697 (22.9)	0.3
Direct oral anticoagulants	22 (3.4)	119 (4.8)	146 (6.3)	20 (2.9)	83 (6.6)	390 (5.3)	0.02
Vitamin K antagonists	229 (35.4)	956 (38.4)	749 (32.1)	199 (29.1)	290 (23.1)	2423 (32.7)	<0.0001
Comorbidity							
Bleeding	136 (21.1)	435 (17.5)	373 (16.0)	108 (15.8)	138 (11.0)	1190 (16.1)	<0.0001
Cancer	89 (13.8)	348 (14.0)	312 (13.4)	76 (11.1)	155 (12.4)	980 (13.2)	0.08
Chronic obstructive pulmonary disease	53 (8.2)	192 (7.7)	208 (8.9)	59 (8.6)	98 (7.8)	610 (8.2)	0.8
Diabetes	117 (18.1)	380 (15.2)	344 (14.8)	105 (15.3)	161 (12.8)	1107 (14.9)	0.007
Hypertension	348 (53.9)	1303 (52.3)	1190 (51.1)	365 (53.3)	702 (55.9)	3908 (52.8)	0.1
Hyperthyroidism	13 (2.0)	89 (3.6)	73 (3.1)	24 (3.5)	28 (2.2)	227 (3.1)	0.3
Ischaemic heart disease	171 (26.5)	647 (26.0)	513 (22.0)	138 (20.1)	175 (13.9)	1644 (22.2)	<0.0001
Kidney disease	34 (5.3)	92 (3.7)	67 (2.9)	20 (2.9)	28 (2.2)	241 (3.3)	0.0004
Prior stroke	134 (20.7)	468 (18.8)	351 (15.1)	104 (15.2)	135 (10.8)	1192 (16.1)	<0.0001

bpm, beats per minute; AF, atrial fibrillation; ECG, electrocardiogram.

median ventricular rate was 83 bpm (IQR = 71–101). Patient characteristics are listed in *Table 1*. A total of 8.7% patients with AF had a ventricular rate <60 bpm, 33.6% between 60 and 79 bpm, 31.5% between 80 and 99 bpm, 9.3% between 100 and 110 bpm, and 16.9% > 110 bpm. At the time of inclusion, a total of 39.1% of patients with AF were in treatment with a beta-blocker, 27.4% with digoxin, 8.9% with verapamil or diltiazem, and 24.6% with ≥2 rate control drugs. At time of ECG recording, 58% of all included patients presenting with AF on ECG had a prior AF hospitalization with a median time from AF hospitalization to ECG recording of 4 years (IQR = 2–8 years). Time from first AF hospitalization to ECG recording is depicted in Supplementary material online, *Figure S1*.

Patients with AF ventricular rate >110 bpm were younger (median age 75 years; IQR = 67–82 years), more likely to be women (58.8%), had fewer comorbidities, and were more likely to be in monotherapy with beta-blockers compared with other ventricular rate groups (*Table 1*). In contrast, patients with AF ventricular rate <60 bpm tended to be older (median age 81 years; IQR = 74–87 years), had a greater comorbidity burden, and were more likely to be in monotherapy with digoxin (*Table 1*). Patients with AF ventricular rate 60–79 bpm were more likely to be in treatment with two rate-control drugs.

At time of ECG recording, 38% of all patients with AF were in anticoagulant therapy with either vitamin K antagonists or direct oral anticoagulants, a number which increased to 57% in the following 6 months.

Baseline characteristics according to type of rate control pharmacotherapy are listed in Supplementary material online, *Table S2*.

Baseline characteristics according to gender are listed in Supplementary material online, *Table S3*.

Risk of heart failure

During the 1-year follow-up period, 666 (9.0%) of all patients with AF developed HF. HF hospitalization according to ventricular rate group are listed in *Table 2*.

The adjusted 1-year standardized absolute risks for new-onset HF according to ventricular rate are depicted in Supplementary material online, *Figure S2*. Patients with AF ventricular rate 100–110 bpm and >110 bpm had an adjusted 1-year standardized absolute risk difference of 2.8% (CI: 0.4–5.3%) and 8.6% (CI: 6.3–10.9%) respectively for new-onset HF compared with patients with AF ventricular rate 60–79 bpm (*Figure 1*).

Restricted cubic spline with three knots for 1-year risk of new-onset HF with ventricular rate as a continuous variable showed no difference in risk of developing new-onset HF among patients with AF ventricular rates 50–100 bpm (*Figure 2*). A dose-response manner for risk of developing new-onset HF was observed among patients with AF ventricular rate >100 bpm (i.e. higher ventricular rate was significantly associated with greater HF risk).

One-year absolute risks for new-onset HF according to rate control pharmacotherapy are depicted in Supplementary material online, *Figures S3 and S4*. Patients with AF on ≥2 rate control drugs had an adjusted 1-year standardized absolute risk difference of −1.8% [CI: −3.5%–(−0.1)%] for new-onset HF, compared with patients with AF on beta-blockers.

According to the multivariable Cox regression analysis, patients with AF ventricular rate 100–110 bpm and >110 bpm had a HR of 1.46 (CI: 1.10–1.95) and 2.41 (CI: 1.94–3.00) respectively for new-onset HF, compared with patients with AF ventricular rate 60–79 bpm. Other significant risk factors included advancing age, hypertension, and IHD (see Supplementary material online, *Figure S5*).

Risk of mortality

During the 1-year follow-up period, 858 (11.6%) of all patients died where 365 patients (43%) had a cardiovascular cause for primary cause of death. Mortality during one year of follow-up according to ventricular rate group is listed in *Table 2*.

The adjusted standardized 1-year absolute risk for all-cause mortality according to ventricular rate is depicted in Supplementary material online, *Figure S2*. Patients with AF ventricular rate 100–110 bpm and >110 bpm had an adjusted 1-year standardized absolute risk difference of 4.0% (CI: 1.2–6.9%) and 3.2% (CI:0.8–5.5%) respectively, compared with patients with AF ventricular rate 60–79 bpm (*Figure 1*).

Restricted cubic spline with three knots for 1-year risk of mortality with ventricular rate as a continuous variable showed a dose-response manner among patients with AF ventricular rate >100 bpm (i.e. higher ventricular rate was associated with greater mortality risk) (*Figure 3*). A widening in confidence intervals was observed for AF ventricular rates >110 bpm.

Results from the 1-year absolute risk analyses for mortality according to rate control pharmacotherapy are depicted in Supplementary material online, *Figures S3 and S4*. Patients with AF on digoxin and ≥2 rate control drugs had an adjusted 1-year standardized absolute risk difference of 4.5 (CI: 2.4–6.5%) and 3.5 (CI: 1.6–5.3%) for mortality respectively, compared with patients with AF on beta-blockers.

According to the multivariable Cox regression analysis patients with AF ventricular rate 100–110 bpm and >110 bpm had a HR of 1.44 (CI: 1.13–1.82) and 1.34 (CI: 1.08–1.65) respectively for all-cause mortality, compared with patients with AF ventricular rate 60–79 bpm (see Supplementary material online, *Figure S6*). Other significant risk factors included male gender, advancing age, diabetes, IHD, and prior history of stroke.

According to the landmark analysis for one-year mortality starting from second year after date of ECG recording, ventricular rate 100–110 bpm and >110 bpm were not associated with excess mortality (see Supplementary material online, *Table S4*).

Sensitivity analyses

To test the robustness of our findings, we performed five additional sensitivity analyses which all yielded similar results as the main findings. For details, see the supplementary material online, *table S5, S6, S7, S8, and S9*.

Discussion

This study of ventricular rate among all-comer patients presenting with AF on first time ECG in rate control pharmacotherapy and risk

Table 2 Heart failure hospitalization and mortality during one year of follow-up according to ventricular rate

	<60 bpm (*n* = 646)	60–79 bpm (*n* = 2492)	80–99 bpm (*n* = 2330)	100–110 bpm (*n* = 685)	>110 bpm (*n* = 1255)	Total (*n* = 7408)	*P*-value
HF hospitalization	62 (9.6)	174 (7.0)	188 (8.1)	65 (9.5)	177 (14.1)	666 (9.0)	<0.0001
Mortality	90 (13.9)	289 (11.6)	254 (10.9)	92 (13.4)	133 (10.6)	858 (11.6)	0.2

HF, heart failure; bpm, beats per minute.

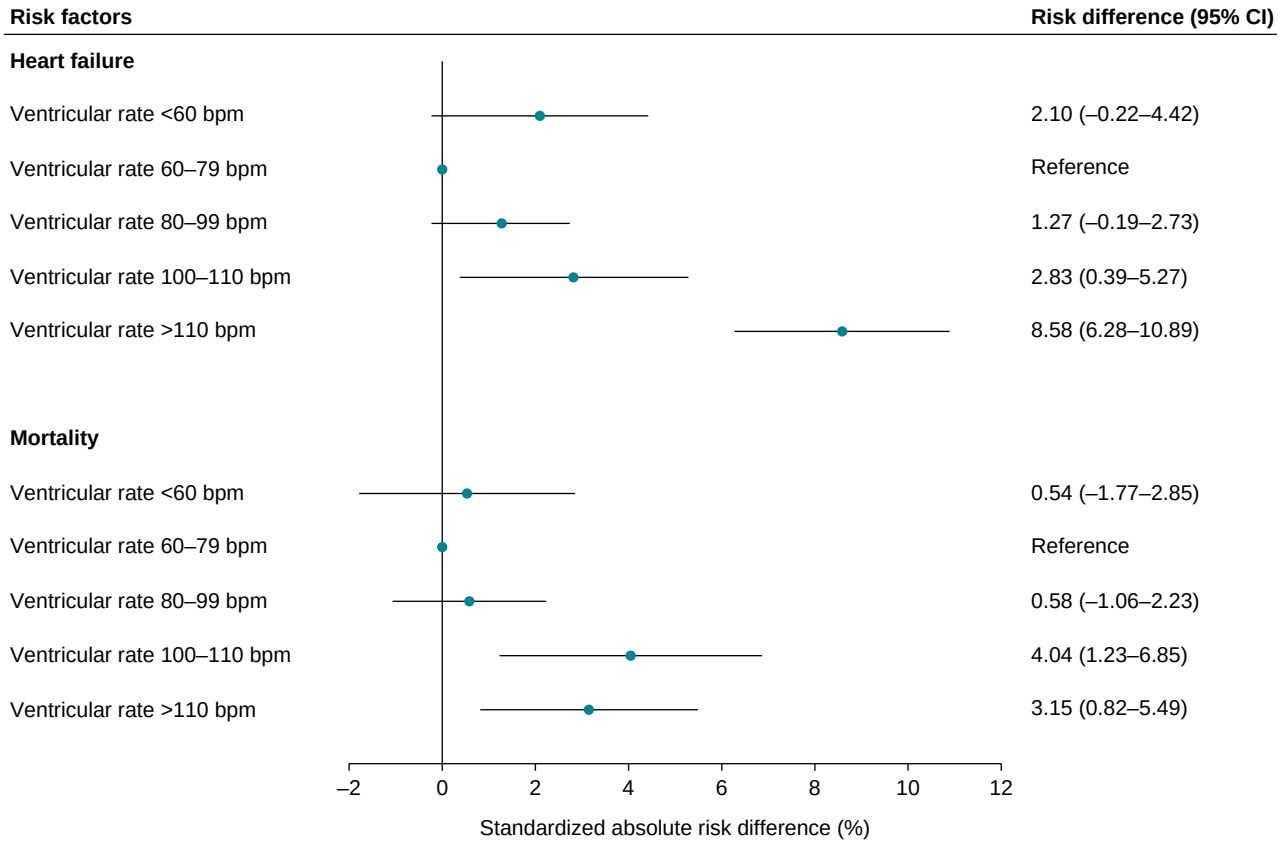


Figure 1 Standardized 1-year absolute risk differences for new-onset heart failure and all-cause mortality according to ventricular rate among patients with atrial fibrillation in rate control pharmacotherapy. Standardized to sex, 5-year increment in age, year of performed ECG, prescription of beta-blockers, verapamil or diltiazem, digoxin, anticoagulants, renin angiotensin system inhibitors, statins, diabetes, hypertension, IHD, kidney disease, and stroke.

of new-onset HF and all-cause mortality had three principal findings. First, 11.6% of all patients with AF died during one year of follow-up whereas 9.0% developed new-onset HF. Second, patients with AF ventricular rates ≥100 bpm associated with increased risk of new-onset HF in a dose-response manner (i.e. higher ventricular rate was significantly associated with greater HF risk). In contrast, patients with AF ventricular rates <100 bpm were not associated with increased HF risk. Third, patients with AF ventricular rates ≥100 bpm were also associated with increased risk of 1-year mortality.

In the present study, AF ventricular rate ≥100 bpm was associated with increased risk of new-onset HF within one year of follow-up. While the AFFIRM trial suggested a mortality benefit in management of AF with rate control over rhythm control, the RACE II trial found that lenient rate-control strategy (resting heart rate <110 bpm) was non-inferior to a strict rate-control strategy (resting heart rate <80 bpm and heart rate during moderate exercise <110 bpm) in terms of preventing the composite outcome of cardiovascular death, HF hospitalization, stroke, systemic embolism, bleeding, and life threatening arrhythmic during three years of follow-up.[3,15] Although we were unable to determine the underlying mechanism of HF development in the present study, the study findings on increased ventricular rate and HF development are in accordance with previous findings on risk of tachycardia induced cardiomyopathy and subsequent development of HF and highlights the importance of ventricular rate management among patients with AF.[16] Collectively, the findings of the present study suggest that a higher ventricular rate in patients with AF in rate control medication could be a red flag and clinical predictor of developing HF which warrants closer monitoring of patients with a high ventricular rate. Though, further investigation is warranted.

A total of 11.6% of patients with AF died during 1-year follow-up in the present study. Importantly, patients with AF ventricular rates ≥100 bpm were associated with increased risk of mortality, whereas patients with AF ventricular rates <100 bpm were not associated with increased risk of mortality. A combined substudy with data from the AFFIRM and Rhythm Control vs. Rate Control for Atrial Fibrillation and Heart Failure trial also found that an elevated baseline ventricular rate in patients with non-permanent AF who were in sinus rhythm when the ECG was performed was associated with increased all-cause and cardiovascular mortality during the first two years of follow-up.[6] In the present study, patients with AF ventricular rate >110 bpm had the lowest median age, were more likely to be female, and had fewer comorbidities compared with the other ventricular rate groups, but were still associated with increased risk of 1-year mortality. In contrast, patients with AF ventricular rate <60 bpm, in the present study, were not associated with increased risk of new-onset HF or all-cause mortality despite these patients were more likely to be male, older, and more comorbid.

Treatment with digoxin for patients with AF and risk of mortality has been debated previously.[17] Recent findings from the RATE-AF trial showed no difference in 6-month ventricular rate and patient-reported

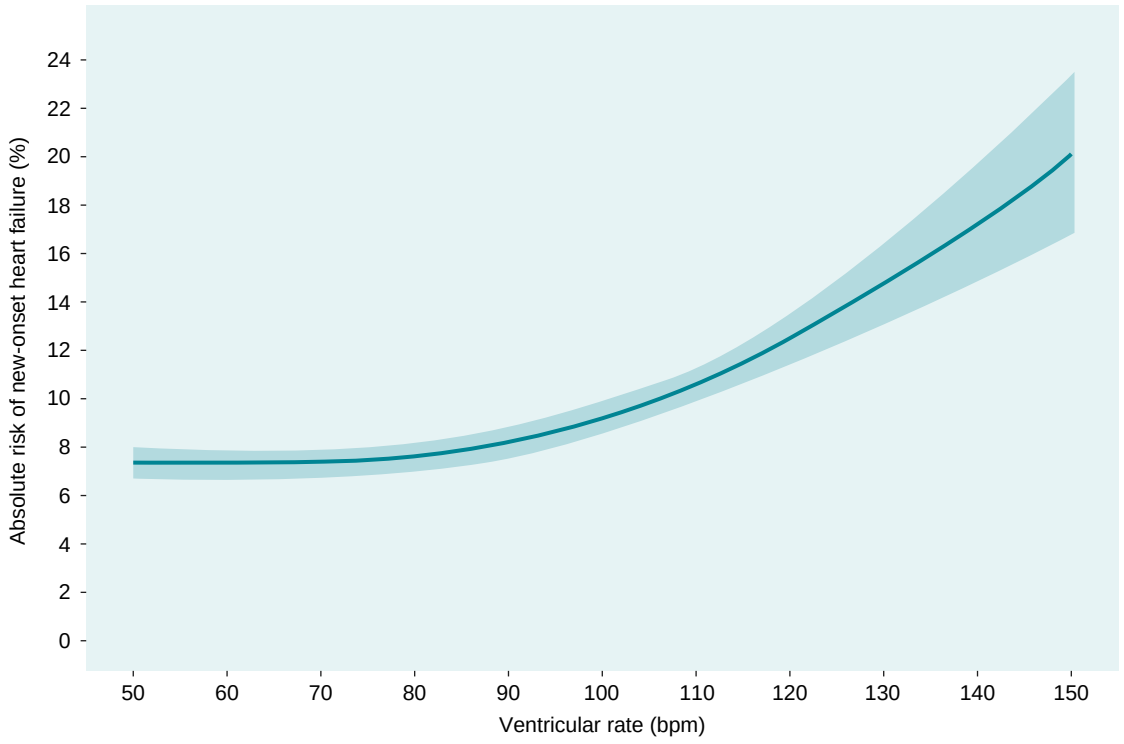


Figure 2 Restricted cubic spline with three knots for 1-year risk of new-onset heart failure according to ventricular rate as a continuous variable among patients with atrial fibrillation in rate control pharmacotherapy. Standardized to sex, 5-year increment in age, year of performed ECG, prescription of beta-blockers, verapamil or diltiazem, digoxin, anticoagulants, renin angiotensin system inhibitors, statins, diabetes, hypertension, IHD, kidney disease, and stroke.

quality of life among patients with permanent AF chosen for treatment with bisoprolol or digoxin and suggested that digoxin could be first-line treatment for patients with permanent AF.[18] Interestingly, patients chosen for treatment with digoxin had a significant better 12 month improvement in N-terminal pro B-type natriuretic peptide, and AF and HF symptom scores compared to patients chosen for treatment with bisoprolol. Although the trial was not powered for clinical events, fewer all-cause deaths and cardiovascular deaths were reported in the digoxin group. These findings conflict with the findings from our study where patients on digoxin or ≥2 rate control drugs were associated with increased risk of mortality. However, patients on digoxin or ≥2 rate control drugs tended to be older and had a greater comorbidity-burden.

The present study utilized ECGs recorded at The Copenhagen General Practitioners' Laboratory and which were analysed utilizing version 23 of the Marquette 12SL program that has a high sensitivity (87.5%) and specificity (99.4%). While a recent study conducted by De Bie *et al.*[19] found that the version 22 of the Marquette 12SL program had the lowest false-positive rate and a low false-negative rate for detecting AF compared with six other ECG analysing programs, all seven ECG analysing programs had increased false-positive and false-negative rates with increases in high heart rate ≥100 bpm.

Strengths and limitations

Due to the observational study design no causal inference should be made but rather interpreted as associations. Therefore, risk of confounding by indication and residual confounding cannot be ruled out, although we tried to eliminate the effect of these. Also, we acknowledge renal function affects outcomes of the present study. Despite, we had national data on all in and outpatients hospital admissions, it is possible that some patients had known renal disease and were managed solely by their primary care physician. Furthermore, laboratory data, (e.g. glomerular filtration rate, creatinine, and carbamide), were not available in our national registries which may likely have led to an underestimation of the prevalence of renal disease in our study. The present study included ECGs presenting with AF ventricular rate ≥100 bpm which may have affected the Marquette 12SL programs interpretation of the ECGs. We acknowledge that using the presenting ventricular rate on first-time ECG recording showing AF for our analyses may have affected our results. Moreover, ventricular rates recorded on ECGs only represent a short duration of the ventricular rate at time of recording. Also, a second ECG recording during one year of follow-up was not available, and we acknowledge the inability to conclude if ventricular rate was chronically elevated during follow-up. Though, we found a strong association between elevated AF ventricular rate and risk of developing HF and mortality, despite we only used a 10 s ECG recording for our analyses, which suggests there might be an even stronger association. We acknowledge that indication for ECG recording and the circumstances when the ECG were recorded in the setting of primary care were unknown and therefore ECGs might have been recorded on a clinical indication, and higher ventricular rates could be a marker of sicker patients, and in principle existing HF. Though, we acknowledge the inability to conclude whether HF outcomes were driven by high ventricular rate or high ventricular rate were driven by unknown pre-existing HF. Furthermore, we acknowledge the inability to conclude whether mortality outcomes were driven by high ventricular rate or a high ventricular rate was a marker for sicker patients. Also, data on whether ventricular rate on ECG

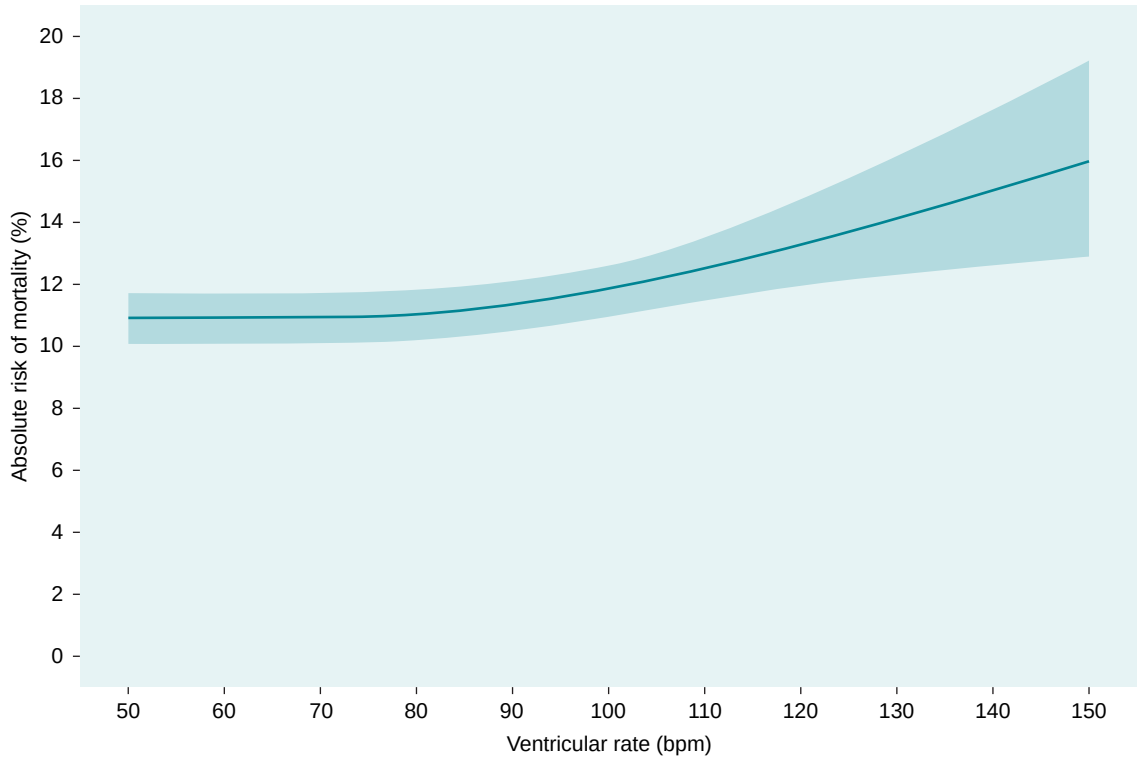


Figure 3 Restricted cubic spline with three knots for 1-years risk of mortality according to ventricular rate as a continuous variable among patients with atrial fibrillation in rate control pharmacotherapy. Standardized to sex, 5-year increment in age, year of performed ECG, prescription of beta-blockers, verapamil or diltiazem, digoxin, anticoagulants, renin angiotensin system inhibitors, statins, diabetes, hypertension, IHD, kidney disease, and stroke.

were resting condition or not, duration of ECG recording, ventricular rate over time, ventricular rate during follow-up, and type of AF were not available. The indication for rate control drugs at time of ECG recording was not available. Information on how specific follow-up after time of ECG was not readily available and may have influenced our findings. Despite the algorithm utilized to analyse ECG recordings in the present study have a high sensitivity and specificity for diagnosing of AF, we acknowledge the inability to manually adjudicate ECGs. Also, we acknowledge that the inability to track changes in rate- or rhythm-control strategies in response to the initial ECG may have influenced our findings which is a limitation of the present study. The study population were in general older and therefore the findings of the present study are not generalizable to younger patients with AF. Despite we excluded patients with known HF, it is possible that patients may have had undiagnosed HF at the time of ECG recording which may have affected the findings of the study. Despite, results from our sensitivity analyses where patients in pharmacological treatment with drugs commonly used to treat HF were excluded yielded similar results as the main analysis, we acknowledge that using diagnosis codes for identification of HF hospitalizations to define new-onset of HF during follow-up is a major limitation of the present study. Also, a limitation of the present study is the inability to determine aetiology of HF (i.e. ischaemic or non-ischaemic). We found an association between patients with AF ventricular rate >110 bpm and increased risk of new-onset HF and mortality despite this group tended to be younger, women, and less comorbid. Though, patients with AF ventricular rate >110 bpm had the highest proportion of atrial flutter which may have affected the findings of the study. However, results from our sensitivity analyses where patients with atrial flutter were excluded yielded similar results as the main analysis. Also, patients with AF ventricular rate >110 bpm were more likely to be in monotherapy with beta-blockers, calcium channel blockers, or digoxin compared to other ventricular rate groups. It is possible these patients had the highest AF ventricular rate at time of ECG recording due to an inadequate rate control. We acknowledge that the CHA_2 DS_2-VASc and HAS-BLED scores of the included patients may have influenced the treating physician's decision on anticoagulants. Though, all data needed for these scores were not available in our national registries. Also, due to the design of the present study, we acknowledge the inability to conclude on how many patients in medical therapy with vitamin K antagonists that were in therapeutic range at date of ECG recording.

Conclusion

Among patients with AF managed with a rate-control drug according to Danish nation-wide registries, a ventricular rate ≥100 bpm was associated with increased 1-year risk of new-onset HF in a dose-response manner (i.e. higher ventricular rate was significantly associated with greater HF risk). In addition, patients with AF ventricular rates ≥100 bpm were also associated with a greater risk of 1-year mortality.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

Data for this study are derived from Statistics Denmark. By law, these data are not allowed to be shared. Therefore, data cannot be made available to other researchers.

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