Simpson, Joanne; Castagno, Davide; Doughty, Rob N.; Poppe, Katrina K.; Earle, Nikki; Squire, Iain; Richards, Mark; Andersson, Bert; Ezekowitz, Justin A.; Komajda, Michel; Petrie, Mark C.; Mcalister, Finlay A.; Gamble, Greg D.; Whalley, Gillian A.; Mcmurray, John J.V. Is heart rate a risk marker in patients with chronic heart failure and concomitant atrial fibrillation? Results from the MAGGIC meta-analysis. EUROPEAN JOURNAL OF HEART FAILURE. 17 (11) pp: 1182-1191.
DOI: 10.1002/ejhf.346

Is heart rate a risk marker in patients with chronic heart failure and concomitant atrial fibrillation? Results from the MAGGIC meta-analysis

Simpson J, Castagno D, Doughty RN, Poppe KK, Earle N, Squire I, Richards M, Andersson B, Ezekowitz JA, Komajda M, Petrie MC, McAlister FA, Gamble GD, Whalley GA, McMurray JJ; Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC).

Abstract

Aim

To investigate the relationship between heart rate and survival in patients with heart failure (HF) and coexisting atrial fibrillation (AF).

Methods and Results

Patients with AF included in the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) meta-analysis were the main focus of this analysis (3259 patients from 17 studies). The outcome was all-cause mortality at 3 years. Heart rate was analysed as a categorical (tertiles; T1 ≤77 b.p.m., T2 78–98 b.p.m., T3 ≥98 b.p.m.) and continuous variable. Cox proportional hazard models were used to compare the risk of all-cause death between tertiles of baseline heart rate. Patients in the highest tertile were more often female, less likely to have an ischaemic aetiology or diabetes, had a lower ejection fraction but higher blood pressure and New York Heart Association (NYHA) class. Higher heart rate was associated with higher mortality in patients with sinus rhythm (SR) but not in those in AF. In patients with heart failure and reduced ejection fraction (HF-REF) and AF, death rates per 100 patient years were lowest in the highest heart rate tertile (T1 18.9 vs. T3 15.9) but this difference was not statistically significant (P = 0.10). In patients with heart failure and preserved ejection fraction (HF-PEF), death rates per 100 patient years were highest in the highest heart rate tertile (T1 14.6 vs. T3 16.0, P = 0.014). However, after adjustment for other important prognostic variables, higher heart rate was no longer associated with higher mortality in HF-PEF (or HF-REF).

Conclusions

In this meta-analysis of patients with HF, heart rate does not have the same prognostic significance in patients in AF as it does in those in SR, irrespective of ejection fraction or treatment with beta-blocker.

Introduction

Elevated resting heart rate is an established marker of adverse outcome in apparently healthy individuals and in patients with a wide spectrum of cardiovascular disease, including chronic heart failure (HF).[1, 2] Higher resting heart rate is independently associated with an adverse prognosis in patients with heart failure and reduced ejection fraction (HF-REF) in sinus rhythm.[3] Moreover, reducing heart rate in patients with HF-REF in sinus rhythm improves clinical outcomes.[4, 5] Higher heart rate is also associated with higher mortality and morbidity in patients with HF and preserved ejection fraction (HF-PEF) in sinus rhythm, although it is not known whether reducing heart rate improves outcome in these patients[6].

Atrial fibrillation (AF) is present in up to 50% of patients with HF and is associated with worse cardiovascular outcomes compared with sinus rhythm.[7-12] Whether the relationship between 'heart' rate (ventricular rate) and prognosis in patients with HF-REF and concomitant AF parallels that seen in patients with sinus rhythm is not well studied. Even less is known about the association between heart rate in AF and outcomes in patients with HF-PEF. Indeed, the limited evidence available suggests that there might even be an inverse association between heart rate and adverse outcomes in patients with coexistent HF

and AF.[13] This is an important clinical issue as current treatment guidelines advocate a rate control based approach management of AF in HF although there are no robust data to suggest an advantage of strict rate control over lenient rate control in AF.[14-16]

The Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) collated individual patient data from 31 studies and provided the opportunity to examine the relationship between heart rate and prognosis in patients with co-existing AF and both types of HF: HF-REF and HF-PEF.

Methods

Study design

The rationale, design, and results of the MAGGIC meta-analysis have been described in detail previously.[17] In summary, a literature search of Embase, Medline, Medline-In-Progress, and PubMed was performed for observational studies and randomized controlled trials published up to and including 2008. Keywords used to outline the search were: prognosis, outcome, heart failure, left ventricle and preserved. Studies were eligible for inclusion if they adopted a prospective study design, included patients with HF, reported all-cause mortality and if ejection fraction was not used as entry criterion for the study. Each individual study was approved by a local ethics committee and the meta-analysis was approved by The University of Auckland Human Subjects Ethics Committee.

Thirty-one principal investigators contributed study data for the meta-analysis from 56 potential studies identified. These data included demographics, medical history, aetiology, medical treatment, symptom status, clinical variables, laboratory variables, and outcomes. For the present analysis data were available from 21 studies that included patients in sinus rhythm (18 795 patients) and 17 studies that included patients with atrial fibrillation (3259 patients). Details of the studies including patients with AF in this analysis are shown in *Table* 1.[18-34]

Table 1. Features of the 17 studies containing patients with atrial fibrillation (AF) included in the analysis

Study name or lead author	Years patients recruited	Type of study	Country/region	Total patients, *n*	Definition of HF	Key HF groups excluded	Patients with AF, *n* (%)	Duration of follow up (months)
AHFMS[18]	1996–1997	Cluster randomized controlled trial	New Zealand	197	Typical signs and symptoms of HF, with review of the CXR, ECG and echocardiogram	Surgically remediable cause of HF such as severe AS, or if being considered for cardiac transplantation	64 (32)	12
Andersson[19]	1980–1987	Retrospective survey for recruitment, prospective observational follow up	Sweden	149	Diagnosis of HF in hospital record plus one of: pulmonary rales, pulmonary congestion on CXR, peripheral oedema of probable cardiac origin, significant weight loss after diuresis,	Any identifiable cause of HF History of MI or CAD on coronary angiography (personal communication)	–	84

1. AS, aortic stenosis; CAD, coronary artery disease; CHF, congestive heart failure; CXR, chest X-ray; ECG, electrocardiogram; EF, ejection fraction; ESC, European Society of Cardiology; HF, heart failure; LV, left ventricular; MI, myocardial infarction; NT-proBNP, *N*-terminal-pro brain natriuretic peptide; NYHA, New York Heart Association.

Study name or lead author	Years patients recruited	Type of study	Country/region	Total patients, *n*	Definition of HF	Key HF groups excluded	Patients with AF, *n* (%)	Duration of follow up (months)
					cardiogenic shock			
BATTLESCARRED[20]	2001–2006	Randomized controlled trial	New Zealand	364	Framingham or ESC HF guidelines, and immediate pre-randomization NT-proBNP >50 pmol/L	MI with acute revascularization and a subsequent EF during the index admission of >40%, severe valvular disease being considered for surgery, severe AS, HF secondary to mitral stenosis, acute myocarditis or pericarditis, under consideration for heart transplantation	–	36
ECHOS[21]	2001–2002	Randomized controlled trial	Denmark	1000	Dyspnoea (NYHA class II–IV, with class II required to have had ≥1 episode of dyspnoea of Class III or IV within previous month) and pre-existing or presumed new-onset HF, and all patients had received diuretic treatment on admission to the hospital	Significant obstructive valve disease or obstructive cardiomyopathy, MI and/or cardiac revascularization within previous 1 month	(24)	Minimum 12
EuroHeart Survey[22]	2000–2001	Observational	International	6806	At least one of: a clinical diagnosis of HF during admission or at any time in last 3 years; loop diuretic for any reason other than renal failure during 24 h of death or discharge; pharmacological treatment for HF or ventricular dysfunction within 24 h of death or discharge		1622 (24)	–
Gotsman[23]	2001–2002	Prospective observational	Israel	289	HF defined by the treating physician and corroborated by clinical signs and symptoms consistent with HF, reduced LV		97 (34)	12

Study name or lead author	Years patients recruited	Type of study	Country/region	Total patients, *n*	Definition of HF	Key HF groups excluded	Patients with AF, *n* (%)	Duration of follow up (months)
					function by echo, or both			
Grigorian Shamagian[24]	1991–2002	Prospective observational	Spain	416	Framingham and assessment of LV function		(39)	30
HFC Edmonton[25]	1989–1996	Prospective observational	Canada	566	Framingham		(29)	17
Hillingdon[26]	1995–1996	Population-based prospective observational study	UK	220	ESC HF guidelines, with a beneficial response to treatment of HF if doubt remained	Previous history of HF	68 (31)	16
Huynh[27]	1999	Prospective randomized trial	USA	282	Pulmonary congestion on CXR, or typical signs and symptoms of HF in conjunction with definite clinical improvement in response to diuresis. Also needed ≥1 of risk factors for early readmission: history of HF, ≥4 admissions for any reason in preceding 5 years, CHF precipitated by acute MI or uncontrolled hypertension		45 (16)	168
IN-CHF[28]	1995–1999	Prospective observational	Italy	5164	ESC HF guidelines	Valve disease, idiopathic HCM	863 (17.4)	12
Macin[29]	1997–2000	Prospective observational	Argentina	328	Framingham	HF associated with ACS	85 (26)	10
Madsen[30]	1988–1990	Prospective observational	Denmark	190	Dyspnoea with rales and/or pulmonary congestion on CXR	Acute MI during admission or within previous 3 months, cor pulmonale, valvular heart disease, chronic lung disease, chronic renal or hepatic failure, planned open heart surgery	36 (18.9)	24.5
MUSIC[31]	2003–2004	Prospective observational	Spain	494	Established symptomatic HF (NYHA class II–IV).	ACS within previous 3 months, severe valve disease amenable for surgical repair, severe pulmonary, hepatic or renal disease	71 (15.6)	30

Study name or lead author	Years patients recruited	Type of study	Country/region	Total patients, *n*	Definition of HF	Key HF groups excluded	Patients with AF, *n* (%)	Duration of follow up (months)
Newton[32]	1998–2001	Retrospective observational	UK	528	First admission of HF as coded in hospital discharge record, validated by documentation of appropriate signs and symptoms, including CXR and response to diuresis if required		118 (25)	42
NPC 1[33]	1999–2001	Randomized controlled trial	New Zealand	305, 77 with HF	ESC HF guidelines	Previous hospital admission with a diagnosis of HF	35 (11)	–
Pilbrow[34]	1997–2000	Prospective observational	New Zealand	451	Framingham or ESC HF guidelines		–	48

Statistical analysis

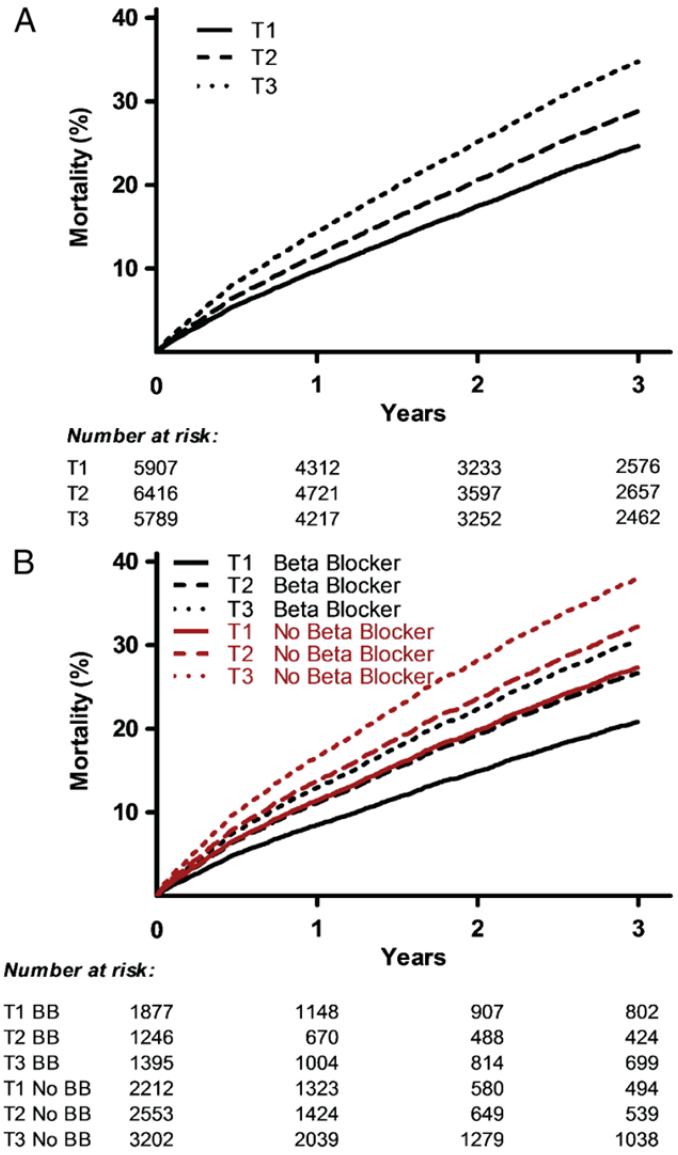
Heart rate (in the case of AF, ventricular rate) was stratified into tertiles and clinical characteristics and outcomes were described for each group. Categorization of heart rhythm was variably based on medical history or the baseline electrocardiogram (ECG) (recruitment/randomization). For inpatient studies, the heart rate closest to discharge was used for the analyses. HF-PEF was defined as an EF ≥50%.[35] The principal outcome was all-cause mortality at 3 years from hospital discharge or baseline study visit. Other outcomes were not available in the MAGGIC dataset.

Baseline characteristics are presented by groups defined by heart rate tertile, with mean and standard deviation (SD) for continuous variables and percentage for categorical variables. Cox proportional hazard models were used to compare the hazard of all-cause death at 3 years between tertiles of baseline heart rate with T1 as the referent tertile. In all cases the models were adjusted for age and sex. In additional models further covariate adjustment was made for the pre-specified MAGGIC prognostic variables: ejection fraction, ischaemic aetiology, hypertension, diabetes, and beta blocker use.[36] Further categorical variables included LVEF subgroup (HF-REF vs. HF-PEF). Models were constructed from those individuals with complete data for each model with no imputation of missing data. The association between baseline heart rate as a continuous variable and risk was also tested in multivariable models. Cumulative survival functions were drawn for the proportional hazards models by solving the function for the average case (without stratifying the model for study). These analyses were performed with outliers removed. Kaplan–Meier survival curves were calculated and all-cause mortality for the three tertiles of heart rate were compared using log rank tests.

Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina, USA). All *P*-values reported are two-sided and $P < 0.05$ was considered statistically significant.

Although the focus of this analysis is AF, the findings from the equivalent analyses for patients in sinus rhythm (which confirm previous reports) are reported in the Supplementary material online for comparison. Adjusted survival analyses for patients in sinus rhythm and for patients in sinus rhythm by beta-blocker use are shown in *Figure* 1A and B, respectively.

Figure 1.



(A) Kaplan–Meier survival analysis in patients in sinus rhythm according to baseline heart rate Event curves for all-cause mortality according to tertiles of baseline heart rate for patients in sinus rhythm, adjusted for age, sex, ejection fraction (EF) group, hypertension, ischaemic aetiology, and diabetes. (B) Kaplan–Meier survival analysis in patients in sinus rhythm according to tertiles of baseline heart rate and beta blocker use. Event curves for all-cause mortality according to tertiles of heart rate with and without beta blocker use adjusted for age, sex, EF group, hypertension, ischaemic aetiology, diabetes

Results

Patients with atrial fibrillation

Data from 17 studies from the MAGGIC meta-analysis provided baseline information on 21361 patients overall. A total of 3259 patients had AF (15.3%) and complete data for 2910 patients were available for the multivariable analysis. 349 patients had missing covariates and were excluded from our analyses.

Baseline characteristics according to heart rate, by tertile

Baseline characteristics according to tertiles of heart rate (≤77 b.p.m., T2 78–98 b.p.m., T3 ≥ 98 b.p.m.) are shown in *Table* 2. Higher heart rate was associated with female sex (T1 vs. T2 vs. T3: 30% vs. 31% vs. 39%, *P*

< 0.0001). Patients with higher heart rate were less likely to have an ischaemic aetiology (T1 vs. T2 .vs. T3: 42% vs. 32% vs. 23%, *P* < 0.0001), a previous myocardial infarction (T1 vs. T2 .vs. T3: 33% vs. 27% vs. 19%, *P* < 0.0001), or diabetes (T1 vs. T2 .vs. T3: 20% vs. 20% vs. 15%). A higher heart rate was also associated with higher New York Heart Association (NYHA) functional class, a higher systolic and diastolic blood pressure and lower ejection fraction.

Table 2. Baseline characteristics according to groups defined by tertiles of baseline heart rate in patients with atrial fibrillation

	T1 (32–76 b.p.m.)	**T2 (77–98 b.p.m.)**	**T3 (99–180 b.p.m.)**	***P*-value (test for trend)**
n (17 studies)	1088	1083	1088	
Age, years (SD)	71 (11)	70 (11)	72 (11)	0.0099
Women, %	30	31	39	<0.0001
Medical history, %				
Hypertension	37	39	34	0.14
Myocardial infarction	33	27	19	<0.0001
Diabetes	20	20	15	0.0017
Ischaemic aetiology	42	32	23	<0.0001
Medication, %				
ACEi or ARB	67	70	61	0.0039
Beta-blocker	35	31	40	0.020
Diuretic	83	84	86	0.13
Spironolactone	27	28	23	0.039
Digoxin	60	66	66	0.0018
Clinical status				
NYHA class (I/II/III/IV)	17/49/28/6	12/52/28/8	12/52/25/12	<0.0001*
Heart rate, b.p.m.	66 (8)	86 (6)	123 (20)	<0.0001
SBP, mmHg, mean (SD)	127 (22)	131 (24)	137 (25)	<0.0001
DBP, mmHg, mean (SD)	75 (12)	78 (14)	83 (16)	<0.0001
LVEF %, median [IQR]	39 [28–54]	37 [27–50]	37 [27–53]	0.016
HF-PEF, %	32	27	30	0.22
All-cause deaths, *n* (%)	260	269	339	0.0006

- ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DBP, diastolic blood pressure; HF-PEF, heart failure with preserved ejection fraction; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; T, tertile.
- *Overall chi-square test, test for linear trend 1,2 vs. 3,4 over tertiles *P* = 0.36.

The patients in the highest heart rate tertile were less often treated with an angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) (T1 vs. T3 67% vs. 61%, respectively) and mineralocorticoid receptor antagonist (27% vs. 23%) but more likely to be treated with a beta-blocker (35% vs. 40%), and digoxin (60% vs. 66%). Although patients with HF-PEF were more likely to be female, older and hypertensive compared with their counterparts with HF-REF, the associations between heart rate tertile and baseline characteristics were similar in both HF subtypes (*Table* 3) as in the overall cohort.

Table 3. Baseline characteristics according to groups defined by tertiles of heart rate, in patients with atrial fibrillation and reduced or preserved ejection fraction [tertiles defined separately in heart failure and reduced ejection fraction (HF-REF) and heart failure and preserved ejection fraction (HF-PEF)]

	HF-REF				HF-PEF			
	T1 (32–77 b.p.m.)	**T2 (78–98 b.p.m.)**	**T3 (>98-180 b.p.m.)**	***P*-value for trend**	**T1 (40–74 b.p.m.)**	**T2 (75–98 b.p.m.)**	**T3 (99–180 b.p.m.)**	***P*-value for trend**
n (17 studies)	758	765	762		318	329	327	
Age, years, mean (SD)	69 (11)	69 (11)	70 (11)	0.13	73 (11)	74 (11)	76 (9)	0.0040
Women, %	20	24	31	<0.0001	50	50	56	0.086
Medical history, %								
Hypertension	32	36	31	0.74	50	46	42	0.051
Myocardial infarction	40	30	22	<0.0001	19	17	11	0.012
Diabetes	20	20	16	0.027	21	19	14	0.020
Ischaemic aetiology	47	35	26	<0.0001	33	26	17	<0.0001
Medication, %								
ACEi or ARB	73	74	69	0.072	57	57	43	0.0004
Beta-blocker	35	32	40	0.036	36	28	37	0.40
Diuretic	81	86	87	0.0056	88	82	84	0.12
Spironolactone	29	31	36	0.35	25	23	17	0.016
Digoxin	64	68	69	0.042	49	60	60	0.0055
Clinical status								
NYHA class (I/II/III/IV)	13/50/31/6	10/51/31/8	10/51/27/12	*0.0010	23/49/23/5	19/50/23/8	17/54/18/10	**0.10
Heart rate, b.p.m., mean (SD)	67 (8)	87 (6)	122 (19)	<0.0001	63 (9)	85 (7)	124 (20)	<0.0001
SBP, mmHg, mean (SD)	125 (21)	129 (22)	134 (25)	<0.0001	135 (24)	138 (28)	142 (26)	0.0064
DBP, mmHg, mean (SD)	74 (12)	78 (13)	82 (16)	<0.0001	76 (12)	78 (16)	84 (16)	<0.0001
LVEF %, median [IQR]	32 [24, 40]	32 [24, 39]	30 [23, 39]	0.015	60 [56 ,62]	60 [54, 62]	60 [56, 60]	0.021
All-cause deaths, *n*	189	190	232	0.048	71	79	107	0.0031
Death rate per 100 patient years, median [IQR]	18.9 [16.3, 21.7]	18.6 [16.1, 21.4]	15.9 [14.0, 18.1]	0.10	14.6 [11.5, 18.3]	15.5 [12.4, 19.3]	16.0 [13.2, 19.2]	0.014

1. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DBP, diastolic blood pressure; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; T, tertile.
2. * test for trend 1 or 2 versus 3 or 4 P = 0.23.

Association between baseline heart rate and all-cause mortality

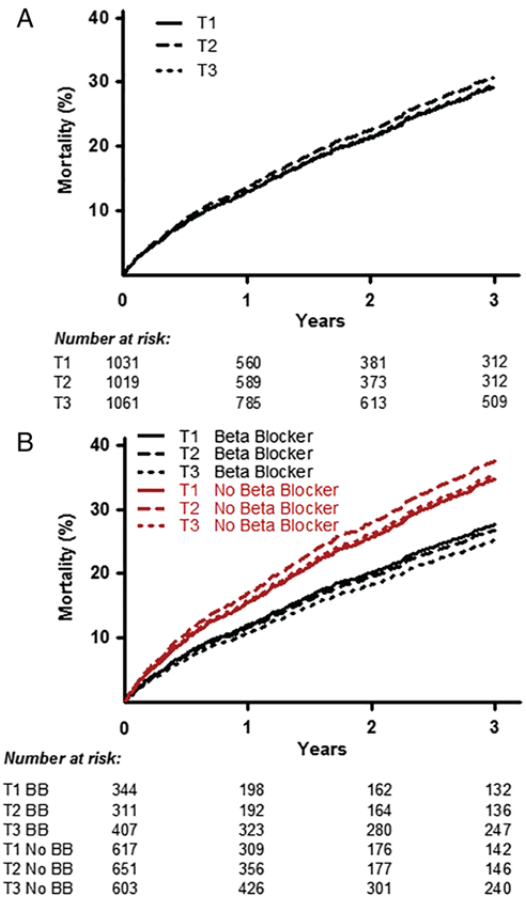
In the 17 studies from the meta-analysis there were 868 deaths (27%) from any cause during 3 years of follow up. Death rates among the HF-REF and HF-PEF groups were 17.8 per 100 patient years and 15.4 per 100 patient years, respectively. In patients with HF-REF, death rates per 100 patient years were lowest in the highest heart rate tertile (T1 18.9 vs. T3 15.9) but this difference was not statistically significant (*P* = 0.10). In patients with HF-PEF, death rates per 100 patient years were highest in the highest heart rate tertile (T1 14.6 vs. T3 16.0, *P* = 0.014) (*Table* 3). However, after adjustment for other important prognostic variables, higher heart rate was no longer associated with higher mortality in HF-PEF (or HF-REF) (*Table* 4, *Figure* 2A). This was true whether or not patients were treated with a beta-blocker at baseline (*Table* 5, *Figure* 2B).

Table 4. Multivariable model by tertiles of heart rate for patients with atrial fibrillation with tertiles (T) defined separately in ejection fraction domain [heart failure and reduced ejection fraction (HF-REF) and heart failure and preserved ejection fraction (HF-PEF)] – adjusted for the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) variables

	Whole group (*n* = 3054)	**HF-REF (*n* = 2115)**	**HF-PEF (*n* = 939)**
Heart rate			
T1	1	1	1
T2	0.99 (0.83, 1.19)	0.94 (0.77, 1.16	1.10 (0.79, 1.53)
T3	0.87 (0.73, 1.04)	0.83 (0.67 1.02)	0.94 (0.68, 1.29)
Age	1.05 (1.04, 1.06)	1.04 (1.03, 1.05)	1.06 (1.04, 1.08)
Female sex	1.37 (1.18, 1.60)	1.35 (1.11, 1.64)	1.39 (1.07, 1.79)
HF-REF	1.31 (1.12, 1.53)	–	–
Hypertension	1.00 (0.87, 1.17)	1.00 (0.83, 1.20)	1.04 (0.79, 1.37)
Ischaemic aetiology	1.35 (1.14, 1.61)	1.42 (1.17, 1.73)	1.12 (0.76, 1.65)
Diabetes	1.38 (1.16, 1.63)	1.40 (1.14, 1.71)	1.31 (0.93, 1.840

1. Data are hazard ratio (95% confidence interval).

Figure 2.



(A) Kaplan–Meier survival analysis in patients with atrial fibrillation (AF) according to baseline heart rate. Event curves for all-cause mortality according to tertiles of baseline heart rate adjusted for age, sex, ejection fraction (EF) group, hypertension, ischaemic aetiology, diabetes. (B) Kaplan–Meier survival analysis in patients with AF according to tertiles of baseline heart rate and beta blocker use. Event curves for all-cause mortality according to tertiles of heart rate with and without beta blocker (BB) use adjusted for age, sex, EF group, hypertension, ischaemic aetiology, and diabetes.

Table 5. Multivariable model including beta blockers by tertiles of heart rate for patients with atrial fibrillation with tertiles (T) defined separately in ejection fraction domain [heart failure and reduced ejection fraction (HF-REF) and heart failure and preserved ejection fraction (HF-PEF)], adjusted for the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) variables

	Whole group (*n* = 2910)	**HF-REF (*n* = 1999)**	**HF-PEF (*n* = 911)**

1. Data are hazard ratio (95% confidence interval).

Heart rate			
T1	1	1	1
T2	0.996 (0.83, 1.19)	0.96 (0.77, 1.19)	1.06 (0.76, 1.49)
T3	0.86 (0.72, 1.03)	0.81 (0.65, 1.00)	0.97 (0.70, 1.34)
Age	1.04 (1.03, 1.05)	1.04 (1.03 1.05)	1.05 (1.04, 1.07)
Female sex	1.35 (1.15, 1.58)	1.34 (1.10, 1.64)	1.30 (1.00, 1.70)
HF-REF	1.39 (1.19, 1.63)	–	–
Hypertension	1.01 (0.86, 1.18)	0.97 (0.81, 1.18)	1.11 (0.84, 1.47)
Ischaemic aetiology	1.41 (1.18, 1.68)	1.46 (1.19, 1.78)	1.19 (0.79, 1.78)
Diabetes	1.35 (1.13, 1.61)	1.41 (1.15, 1.73)	1.20 (0.84, 1.71)
Beta blockers	0.69 (0.59, 0.81)	0.76 (0.63, 0.92)	0.59 (0.44, 0.80)

Heart rate modelled as a continuous variable and all-cause mortality

When heart rate was considered as a continuous variable (in 10 b.p.m. increments), there was a lower risk of death in patients with a higher heart rate in patients with HF-REF (*Table* 6), even after adjusting for the predefined MAGGIC prognostic variables.

Table 6. Multivariable model with heart rate as a continuous variable (in 10 b.p.m. increments) defined separately in ejection fraction domain in patients with atrial fibrillation, adjusted for the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) variables

Heart rate	**Whole group (*n* = 3054)**	**HF-REF (*n* = 2115)**	**HF-PEF (*n* = 939)**

1. Data are hazard ratio (95% confidence interval).
2. HF-PEF, heart failure with preserved ejection fraction; HF-REF, heart failure with reduced ejection fraction.

Per 10 b.p.m. increase	0.96 (0.94, 0.99)	0.95 (0.92, 0.98)	0.99 (0.94, 1.03)
Age	1.05 (1.04, 1.05)	1.04 (1.03, 1.05)	1.06 (1.04, 1.08)
Female sex	1.35 (1.15, 1.57)	1.32 (1.09, 1.61)	1.37 (1.06, 1.78)
HF-REF	1.33 (1.14 1.55)	–	–
Hypertension	1.00 (0.86, 1.17)	0.996 (0.83, 1.19)	1.04 (0.79, 1.37)
Ischaemic aetiology	1.35 (1.13, 1.60)	1.41 (1.16, 1.71)	1.11 (0.75, 1.63)
Diabetes	1.37 (1.16, 1.63)	1.39 (1.14, 1.70)	1.31 (0.93, 1.84

Patients with sinus rhythm

Data from 21 studies from the MAGGIC meta-analysis provided baseline information on 18 795 patients in sinus rhythm. Complete data for 17 571 patients were available for the multivariate analysis. Baseline characteristics according to tertiles of heart rate in patients with sinus rhythm are detailed in the Supplementary material online. Higher heart rate was associated with female sex. Patients with higher heart rates were more likely to have diabetes but less likely to have a previous myocardial infarction or ischaemic aetiology. After adjusting for important prognostic variables, higher heart rate was associated with higher mortality in patients with HF-REF and HF-PEF (*Figure* 1A and the Supplementary material online). This was true whether or not patients were treated with a beta-blocker at baseline (*Figure* 1B). When heart rate was considered as a continuous variable (in 10 b.p.m. increments), there was a higher risk

of death in patients with a higher heart rate in patients with HF-REF and HF-PEF after adjusting for the MAGGIC prognostic variables (all information shown in the Supplementary material online).

Discussion

This analysis from the MAGGIC meta-analysis is the largest to date that describes the relationship between heart rate and prognosis in patients with HF and concomitant AF. Our findings show that heart rate does not have the same prognostic significance in patients with AF as it does in those in sinus rhythm. This study is novel in that is the first to examine the relationship between heart rate and mortality according to EF domain and beta-blocker use.

The prognostic value of heart rate in patients with AF and HF-REF

Our data show that higher heart rates in individuals with HF-REF and AF are not associated with adverse outcomes, contrary to findings in patients with HF-REF and sinus rhythm. The lack of relationship between heart rate and outcomes in patients with HF-REF and concomitant AF has previously been described.[13, 37, 38] Our observation is also consistent with a *post hoc* analysis of a clinical trial showing lenient rate control was associated with similar outcomes to strict rate control in patients with HF-REF and coexisting AF.[16]

There are a number of possible explanations for the findings described above. An increase in ventricular rate may be a compensatory response to the loss in atrial contribution to cardiac output and failure to mount this response may be a bad prognostic sign.[39] Indeed, some patients in the first heart rate tertile in this meta-analysis may have had a relative bradycardia and possible underlying disease of the conducting system, which increases the likelihood of death due to a bradyarrhythmia. While elevated heart rates in sinus rhythm in the setting of HF reflects increased neurohormonal activation and sympathetic tone activating the sinoatrial node, the degree of elevation of the ventricular rate in AF is determined by the level of block at the atrioventricular node. Therefore, the less direct correlation between sympathetic tone and ventricular rate in AF, compared with sinus rhythm, may explain the less clear correlation between ventricular rate and prognosis in patients with HF and AF. It may also be relevant to recent findings on the effectiveness of beta-blockers in HF-REF patients with AF (see below).

Beta blocker use in patients with AF and HF-REF

Beta-blockers are a cornerstone of treatment of HF-REF based on multiple randomized placebo-controlled trials demonstrating reduced mortality compared with placebo.[40-44] However, in a recent meta-analysis including 18 254 patients from placebo-controlled trials of beta-blockers in HF-REF, Kotecha and colleagues[45] showed that this treatment did not improve survival in the large subgroup of 3066 patients with AF, compared with those in sinus rhythm. This study expanded on an earlier published meta-analysis of randomised trials.[46] Our current findings are also consistent with this *post hoc* analysis (in that lower heart rate was not associated with better outcome). Although we found that patients taking a beta-blocker had better survival than those who did not, ours is an observational study and it is likely that patients able to tolerate a beta-blocker were healthier than those unable to take beta-blockers at baseline.

Association between heart rate and outcomes in patients with AF and HF-PEF

In an analysis of the relationship between heart rate and outcomes in the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity)-Preserved trial,[13] patients with AF were not examined separately from patients in sinus rhythm because of the small numbers of individuals (n = 478) with both HF-PEF and AF. Outcomes have been reported in the 696 patients with HF-PEF and concomitant AF included in the I-Preserve (Irbesartan in heart failure with preserved systolic function)[6] trial and no relationship between heart rate clinical events was found in that analysis. The 974 patients with HF-PEF and

AF from the present MAGGIC meta-analysis represent the largest and most robust analysis to date. Interestingly, higher heart rate did not confer worse prognosis in this cohort of patients, unlike in patients with HF-PEF in sinus rhythm where higher heart rate is associated with worse prognosis (and confirmed in the present dataset). Even after adjusting for other factors known to affect prognosis this finding did not change. Similar mechanistic considerations to those described for HF-REF may also be relevant in HF-PEF. Our findings may also question the potential value of beta-blockers in HF-PEF, although the results of a prospective randomized controlled trial are awaited.[47]

Limitations

Limitations inherent to meta-analyses must be considered when interpreting the MAGICC data. The present report describes a retrospective analysis of an individual-patient meta-analysis of a heterogeneous group of studies including clinical trials and registries, with completeness of follow-up in the latter less certain than in the former. While this is one of the largest studies of the prognostic significance of heart rate in patients with HF and AF, the number of patients with HF-PEF was limited and a more modest association between ventricular rate and outcome cannot be excluded.

Categorization of heart rhythm was variably based on medical history or the baseline ECG (at recruitment/randomization). Measurement of rate was made at a single time-point and was not standardized. Heart rhythm may change and the ventricular rate in patients with atrial fibrillation is often labile. Both of these are limitations of this type of study. Moreover, ventricular rate in patients with AF is underestimated if heart rate is recorded by palpation of a peripheral pulse or auscultation rather than an electrocardiograph. Serial measurements of heart rate and medications over time could have provided additional prognostic information. Complete data for other rate lowering medications were not available from all studies and was therefore not included in this analysis. This could have influenced results for patients with lower heart rates. A total of 349 patients could not be included in the current analysis because of missing data.

The clinical outcome of all-cause mortality was the only outcome recorded completely across all studies therefore information on morbidity, such as hospitalizations or quality of life, was not available. Heart rate may well be a prognostic factor for hospitalizations or symptom status.

Conclusion

There is no evidence of an association between heart rate and outcomes in patients with chronic HF and concomitant AF, perhaps explaining why beta-blockers do not appear to exert beneficial effects in HF patients with concomitant AF.[46]

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