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Original research

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ABSTRACT

Objective To investigate heart rate differences between non-dihydropyridine calcium channel blockers and beta-blockers in patients with non-permanent atrial fibrillation (AF).

Methods Using data from 'A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation' (AFFIRM), where patients were randomised 1:1 rate or rhythm control, we compared the effect of rate control drugs on heart rate during AF as well as during sinus rhythm. Multivariable logistic regression was used to adjust for baseline characteristics.

Results A total of 4060 patients were enrolled in the AFFIRM trial, mean age was 70±9 years, 39% were women. Out of the total, 1112 patients were in sinus rhythm at baseline and used either non-dihydropyridine channel blockers or beta-blockers. Of them, 474 had AF during follow-up while remaining on the same rate control drugs, 218 (46%) on calcium channel blockers and 256 (54%) on beta-blockers. Mean age of calcium channel blocker patients was 70±8 years and 68±8 for beta-blocker patients (p=0.003), 42% were women. A resting heart rate <110 beats per min during AF was achieved in 92% of patients using calcium channel blockers and 92% of patients using beta-blockers (p=1.00). Bradycardia during sinus rhythm occurred in 17% of patients using calcium channel blockers vs 32% using beta-blockers (p<0.001). After adjusting for patient characteristics, calcium channel blockers were associated with a reduction in bradycardia during sinus rhythm (OR 0.41, 95% CI 0.19 to 0.90).

Conclusion In patients with non-permanent AF, calcium channel blockers instituted for rate control were associated with less bradycardia during sinus rhythm compared with beta-blockers.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Non-dihydropyridine calcium channel blockers and beta-blockers can both be used to achieve rate control in patients with atrial fibrillation, but their effects on heart rate in patients with paroxysmal atrial fibrillation have rarely been compared.

WHAT THIS STUDY ADDS

⇒ In this study, bradycardia in sinus rhythm occurred significantly more often in patients treated with beta-blockers compared to patients using non-dihydropyridine calcium channel blockers while rate control during atrial fibrillation was comparable.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Non-dihydropyridine calcium channel blockers could be considered as an alternative rate control drug in patients who experience symptomatic bradycardia or other side effects on beta-blockers.

INTRODUCTION

Heart rate control is one of the pillars of the management of atrial fibrillation (AF), and is recommended in all patients with AF to reduce symptoms and prevent the development of heart failure.[1] According to European Society of Cardiology (ESC) guidelines, lenient rate control should be the default, targeting a heart rate <110 beats per min (bpm) and lower if symptoms persist at that initial target.[1] In the absence of important comorbidities such as heart failure with reduced ejection fraction or obstructive pulmonary disease, the guideline recommends to start with either beta-blockers or non-dihydropyridine calcium channel blockers, and no preference is given. Both drugs are equally effective at achieving rate control targets during AF.[2–4] In patients with paroxysmal AF, it is of importance to strive for effective rate control during episodes of AF, without causing symptomatic bradycardia during periods of sinus rhythm. The specific pharmacodynamics of non-dihydropyridine calcium channel blockers may attenuate this risk of symptomatic bradycardia. By selectively slowing conduction in the atrioventricular node, but not the sinus node,[5] calcium channel blockers may have a low risk of bradycardia during sinus rhythm. Beta-blockers on the other hand, reduce the heart rate during sinus rhythm as much as during AF,[6] and as a result lead to exercise intolerance[7] and symptomatic bradycardia during sinus rhythm.[8 9] Surprisingly, there are no large-scale data on heart rate response differences between these agents available in the AF literature. Therefore, we compared non-dihydropyridine calcium channel blockers and beta-blockers with respect to rate control during AF and bradycardia risk in sinus rhythm in patients with non-permanent AF included in the AFFIRM trial.

METHODS

The AFFIRM trial was a multicentre randomised controlled trial comparing rate with rhythm

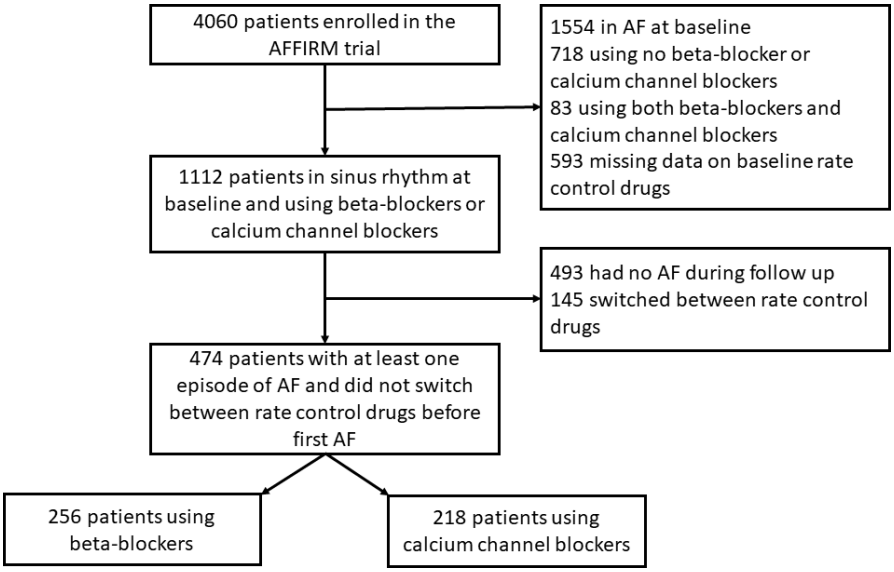

Figure 1 Flow chart displaying patient selection. AF, atrial fibrillation.

control in patients with AF. The trial design was published before.[10] In short, 4060 patients were included in 213 sites in the USA and Canada, and were randomised to either rate control or rhythm control treatment strategy. Within each treatment arm, use of medication was at the discretion of the treating physician. Treatment with beta-blockers or calcium channel blockers was not randomised.

In the current analysis, all patients in sinus rhythm at baseline using either non-dihydropyridine calcium channel blockers or beta-blockers were analysed, patients using both rate control drugs were excluded (n=1112). Patients from both the rate control arm and rhythm control arm were included. Patients who did not have an episode of AF, or switched between rate control drugs before the first episode of AF were excluded (n=638) resulting in a study population of 474 patients (figure 1).

Heart rate assessment

At baseline and during follow-up visits, ventricular heart rate was assessed using electrocardiograms or apical pulse taking. Episodes of AF were confirmed on 12-lead ECG and used to evaluate rate control. Patients were seen by study personnel for data collection at 2 months, 4 months and every 4 months thereafter. The first episode of AF during follow-up was used to evaluate heart rate during AF. The follow-up visit before first AF was used to evaluate heart rate in sinus rhythm (figure 2). Heart rate during AF was used to evaluate whether a resting heart rate <110 bpm (lenient rate control) was achieved.[11] Bradycardia in sinus rhythm was assessed by apical pulse taking or 12-lead ECG, and bradycardia was defined as a heart rate <60 bpm and severe bradycardia as a heart rate <50 bpm. In the rate control arm of the AFFIRM trial, the rate control target during AF was

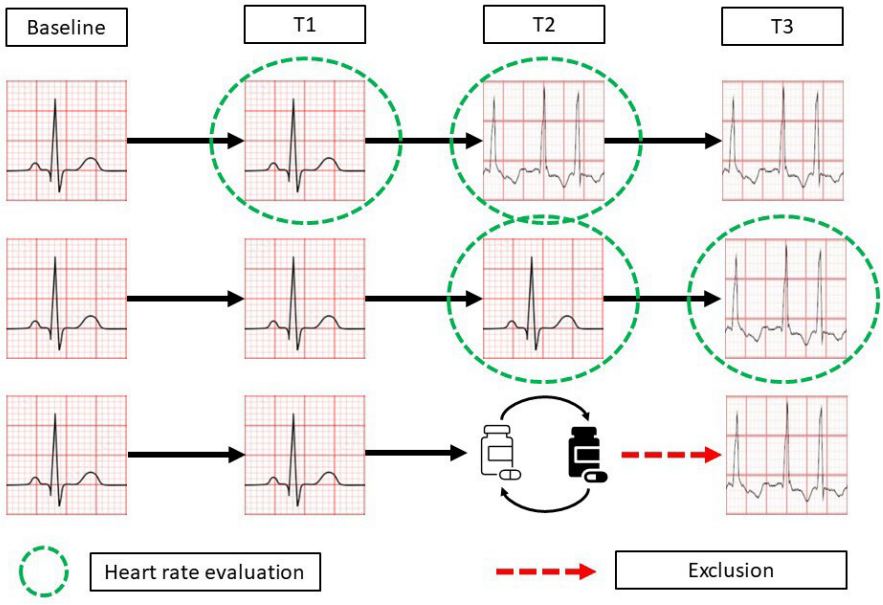

Figure 2 Time points of heart rate evaluation. The first episode of atrial fibrillation (AF) was used to asses heart rate during AF. The visit prior to AF was used to asses heart rate in sinus rhythm. Patients who switched between rate control drugs were excluded.

a resting heart rate <80 bpm and a heart rate <110 bpm during a 6 min walk test.

Statistical analysis

Normally distributed covariates are reported as mean±SD, non-normally distributed covariates as median (IQR) and categorical variables as count (percentage). Differences between baseline covariates were tested using Student's t-test for normally distributed variables and Mann-Whitney U test for non-normally distributed covariates. Fisher's exact test was used to test for differences between categorical covariates. Univariate logistic regression analysis was used for comparisons between the beta-blocker and calcium channel blocker groups. Multivariable logistic regression analysis was used to adjust for differences in baseline characteristics between both groups. We adjusted for age, heart rate at baseline, use of beta-blockers within 6 months prior to randomisation, use of calcium channel blockers within 6 months prior to randomisation, prior bradycardia or atrioventricular block, coronary artery disease, chronic pulmonary disease, concomitant digoxin usage and concomitant amiodarone usage.[12]

We assessed potential multicollinearity in the model using variance inflation factor values and found no signs of multicollinearity. All tests performed were two-sided. Overall, a p value <0.05 was considered to be statistically significant. Data analysis was performed using R statistics (V.4.1.1).

Sensitivity analysis

Several sensitivity analyses were performed to increase the robustness of the model and results. Bradycardia during sinus rhythm was also analysed in patients that were excluded from the main analysis because of the absence of AF during follow-up or a switch in rate control drugs before AF. For patients without AF during follow-up, we used the last follow-up visit prior to the median time to AF from the main population. For patients who switched rate control drugs, we used the last follow-up visit before the switch of rate control drugs.

Stratified analyses were performed based on the randomised treatment arms. The effects of calcium channel blockers and beta-blockers on bradycardia and lenient rate were separately analysed in the rate and rhythm control arm.

Furthermore, a multivariable logistic regression analysis was conducted, incorporating the identical variables employed in the primary analysis, although excluding the baseline heart rate variable. This additional analysis was undertaken to explore the possibility that baseline heart rate is on the causal pathway between rate control treatment and susceptibility to bradycardia or achieving lenient rate control.

RESULTS

Patient characteristics

A total of 1112 of 4060 (27%) patients were in sinus rhythm at baseline and used either non-dihydropyridine channel blockers (509, 46%) or beta-blockers (603, 54%) (figure 1). Of the total, 474 had at least one episode of AF while remaining on the same rate control drugs, 218 (46%) of them using calcium channel blockers (74% diltiazem and 26% verapamil) and 256 (54%) of them using beta-blockers. The mean age was 69±8 years and 44% were women, median time to AF was 119 (62–378) days. Patients using calcium channel blocker were significantly older than patients using beta-blockers (70±8 years vs 68±8 years, respectively, p=0.003, table 1), more often had pulmonary disease and less often coronary heart disease (table 1). The mean heart rate in sinus rhythm at baseline was 69±10 bpm in the calcium channel blocker-treated patients and 66±12 bpm in the beta-blocker-treated patients (p<0.001). History of bradycardia or atrioventricular block as well as concomitant use of digoxin and amiodarone was comparable between patients using calcium channel blockers and patients using beta-blockers. Excluded patients more often used amiodarone but were otherwise comparable to the included patients (table 2).

Table 1 Patient characteristics at baseline

	Calcium channel blockers	Beta-blocker	P value
	N=218	N=256	
Age (years)	70±8	68±8	0.003
Female sex (%)	96 (44)	105 (41)	0.569
BMI	30±6	30±6	0.739
Diastolic blood pressure (mm Hg)	76±10	77±10	0.156
Systolic blood pressure (mm Hg)	138±19	135±19	0.071
Heart rate (bpm)	69±10	66±12	<0.001
History of coronary artery disease (%)	62 (28)	111 (43)	0.001
Hypertension (%)	159 (73)	184 (72)	0.877
Valvular heart disease (%)	27 (12)	36 (14)	0.689
History of stroke (%)	29 (13)	47 (18)	0.171
Diabetes (%)	55 (25)	57 (22)	0.517
History of pulmonary disease (%)	46 (21)	18 (7)	<0.001
Electrical or chemical cardioversion prior to inclusion (%)	20 (16)	13 (8)	0.050
Known bradycardia or atrioventricular block (%)	12 (6)	23 (9)	0.205
Chronic heart failure (%)	39 (18)	58 (23)	0.243
Medication usage at baseline			
Beta-blockers (%)	31 (14)	201 (79)	<0.001
Diltiazem (%)	132 (60)	31 (12)	<0.001
Verapamil (%)	46 (21)	9 (4)	<0.001
Digoxin (%)	117 (54)	118 (46)	0.121
Amiodarone (%)	14 (6)	16 (6)	1.000
Other antihypertensive medication (%)	31 (14)	46 (18)	0.328

BMI, body mass index; bmp, beats per min.

Rate control efficacy in AF and bradycardia in sinus rhythm

At the time of the first AF episode, there was no significant difference in resting heart rate during AF between the groups, the mean resting heart rate was 83±17 bpm in patients using calcium channel blockers and 80±17 bpm in patients using beta-blockers (p=0.058, figure 3, table 3). During the first episode of AF, a resting heart rate <110 bpm was achieved in 201 (92%) of patients using calcium channel blockers and in 236 (92%) of patients using beta-blocker and (p=1.00, figure 4). With adjustment for age, heart rate at baseline, prior symptomatic bradycardia or atrioventricular block, coronary artery disease, chronic pulmonary disease, use of beta-blocker or calcium channel blockers prior to randomisation and concomitant digoxin and amiodarone usage, there was no difference in achieving a heart rate <110 bpm for patients using calcium channel blockers compared with patients using beta-blockers (OR 2.77, 95% CI 0.98 to 7.87, p=0.055, table 4). Resting heart rate during follow-up in sinus rhythm before the first AF episode was significantly higher in patients using calcium

Table 2 Patient characteristics at baseline of included and excluded patients

	Included	Excluded	P value
	N=474	N=638	
Age (years)	69±8	69±8	0.900
Female sex (%)	201 (42)	283 (44)	0.556
Body mass index	30±6	29±6	0.014
Diastolic blood pressure (mm Hg)	77±10	75±10	0.089
Systolic blood pressure (mm Hg)	136±19	136±19	0.758
Heart rate (bpm)	67±11	68±12	0.473
History of coronary artery disease (%)	173 (37)	271 (43)	0.051
Hypertension (%)	343 (72)	474 (74)	0.514
Valvular heart disease (%)	63 (13)	70 (11)	0.278
History of stroke (%)	76 (16)	87 (14)	0.302
Diabetes (%)	112(24)	130 (20)	0.220
History of pulmonary disease (%)	64 (14)	104 (16)	0.229
Electrical or chemical cardioversion prior to inclusion (%)	33 (12)	30 (11)	0.942
Known bradycardia or atrioventricular block (%)	35 (7)	37 (6)	0.348
Chronic heart failure (%)	97 (21)	120 (19)	0.540
Medication usage at baseline			
Beta-blockers (%)	232 (49)	313 (49)	1.000
Diltiazem (%)	163 (34)	226 (35)	0.769
Verapamil (%)	55 (12)	97 (15)	0.101
Digoxin (%)	235 (50)	280 (44)	0.069
Amiodarone (%)	30 (9)	87 (17)	0.001
Other antihypertensive medication (%)	77 (16)	100 (16)	0.862

bpm, beats per min.

channel blockers compared with patients using beta-blocker. The mean heart rate during sinus rhythm in the calcium channel group was 69±12 bpm, compared with 66±11 bpm in the beta-blocker group (p<0.001, figure 3, table 3).

In sinus rhythm before the AF episode, bradycardia (<60 bpm) as well as severe bradycardia (<50 bpm) occurred significantly less often in patients using calcium channel blockers than in patients using beta-blockers (table 2). In sinus rhythm, 36 (17%) patients using calcium channel blockers had bradycardia compared with 81 (32%) patients using beta-blockers (p<0.001, figure 4). Severe sinus bradycardia occurred in 2 (1%) patients using calcium channel blockers and 14 (5%) patients using beta-blockers (p=0.013). After adjusting for differences in patient characteristics, calcium channel blockers usage was associated with a lower risk of bradycardia during sinus rhythm compared with beta-blocker usage (OR 0.41, 95% CI 0.19 to 0.90, p=0.028, table 4).

Sensitivity analyses

Baseline characteristics of the population stratified by randomised treatment arm (ie, rate or rhythm control) can be seen in online supplemental table S1. Out of the total population, 405 patients were allocated to the rate control arm and 69 patients to the rhythm control arm. Results of the rate

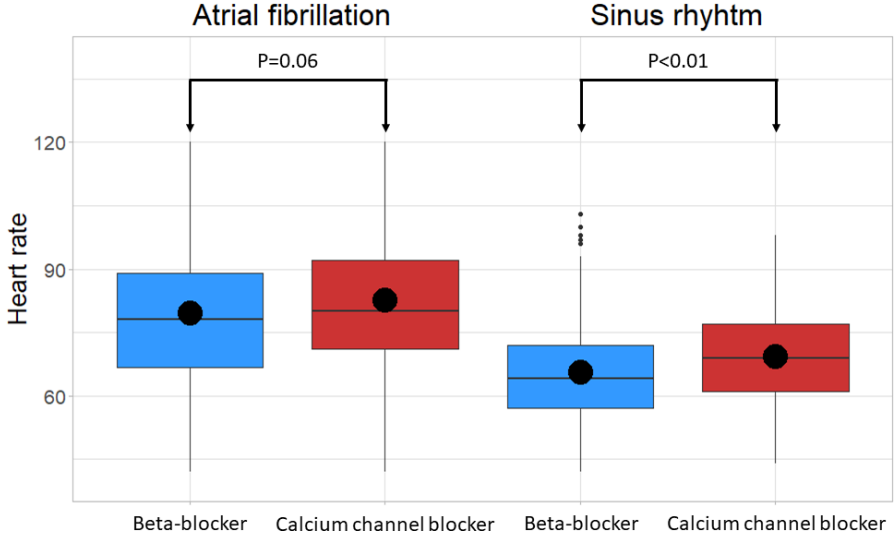

Figure 3 Heart rate during atrial fibrillation and sinus rhythm. Box plot displaying heart rate for patients using beta-blockers and calcium channel blockers in atrial fibrillation and sinus rhythm.

Table 3 Heart rate during follow-up

	Calcium channel blockers N=218	Beta-blockers N=256	P value
Heart rate during AF (bpm±SD)	83±17	80±17	0.058
Heart rate <110 bpm during AF, n (%)	201 (92)	236 (92)	1.000
Heart rate during sinus rhythm (bpm±SD)	69±11	66±12	<0.001
Heart rate <60/min during sinus rhythm, n (% of patients)	36 (17)	81 (32)	<0.001
Heart rate <50/min during sinus rhythm, n (% of patients)	2 (1)	14 (5)	0.013

AF, atrial fibrillation; bpm, beats per min.

Table 4 Logistic regression analysis of the primary outcome

	OR (calcium channel blocker vs beta-blocker)	95% CI
Bradycardia (<60 bpm)		
Univariate analysis	0.43	0.27 to 0.66
Multivariable analysis	0.41	0.19 to 0.90
Lenient rate control (<110 bpm)		
Univariate analysis	1.00	0.51 to 1.99
Multivariable analysis	2.77	0.98 to 7.87

Adjusted for age, heart rate at baseline, use of beta-blockers within 6 months prior to randomisation, use of calcium channel blockers within 6 months prior to randomisation, prior bradycardia or atrioventricular block, coronary artery disease, chronic pulmonary disease, concomitant digoxin usage and concomitant amiodarone usage.
bpm, beats per min; CI, confidence interval; OR, odds ratio.

control arm were comparable to those of the main study population (online supplemental table S2, online supplemental table S3). The rhythm control arm showed no significant differences between the groups.

The sensitivity analysis for heart rate in sinus rhythm that included patients with a rate control drug switch or patients without AF yielded results that were comparable to those of the main population (online supplemental table S4, online supplemental table S5). Additionally, excluding baseline heart rate from the multivariable logistic regression model did not significantly change the main findings (online supplemental table S6).

DISCUSSION

In patients with non-permanent AF, calcium channel blockers and beta-blockers were similarly effective in achieving heart rates <110 bpm during AF, but calcium channel blockers were associated with less bradycardia during sinus rhythm than beta-blockers.

In the ESC AF guidelines, a target heart rate <110 bpm is stated as an acceptable initial approach to rate control.[1] While both calcium channel blockers and beta-blockers are recommended as first-line treatment, there have only been a few small trials comparing these drugs head to head.[13–15] In more recent studies, calcium channel blockers have shown to be at least as effective for rate control during AF as beta-blockers in patients with permanent as well as acute AF.[3 16] These studies however, give no insights into the effects of calcium channel blockers and beta-blockers on heart rate during sinus rhythm periods, especially relevant in the majority of patients with paroxysmal and persistent forms of AF.

Calcium channel blockers only have a modest effect on sinus node automaticity[17] and should in theory, have little effect on heart rate in sinus rhythm. This is in contrast to beta-blockers, which have shown to slow heart rate in sinus rhythm as much as in AF.[6] This may explain our findings that calcium channel blockers cause less (severe) bradycardia in sinus rhythm, in patient with paroxysmal and persistent AF. Due to rapid ventricular rates during AF, rate control drugs often need to be up-titrated to high dosages, however this may increase the risk of bradycardia during prolonged periods of sinus rhythm in these patients. Despite the absence of dosing information in AFFIRM, we observed that the heart rate during sinus rhythm was higher, and also (severe) bradycardia was less prevalent in the patients using calcium channel blockers. Heart rate during AF, however, was comparable and there was no difference in the prevalence of rapid ventricular rate between calcium channel blockers and beta-blockers. The effects of calcium channel blockers and beta-blockers on sinus rhythm heart rate was driven by patients in the rate control treatment arm, as there were no differences in the rhythm control arm. The rhythm control arm was small however, only 69 patients, and therefore lacked the power to draw firm conclusions.

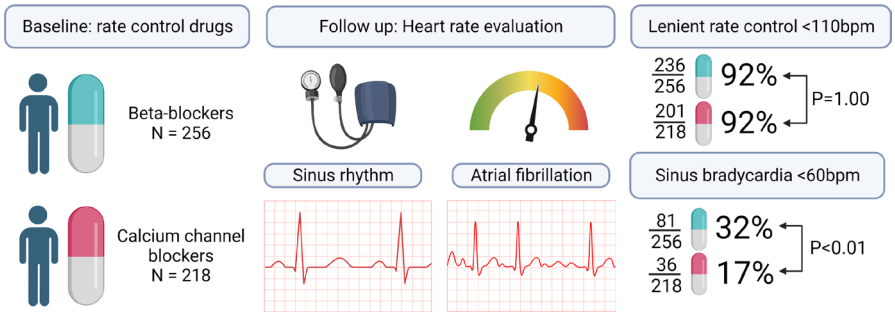

Figure 4 Study design and main results (key figure). Using data from the AFFIRM trial, 256 in sinus rhythm using beta-blockers at baseline and 218 patients in sinus rhythm using calcium channel blockers at baseline were analysed. Heart rate was evaluated during the first episode of atrial fibrillation and in sinus rhythm before atrial fibrillation. In both groups, 92% of patients achieved lenient rate control (heart rate <110 beats per min). Sinus bradycardia (heart rate <60 beats per min) occurred in 32% of patients using beta-blockers and 17% of patients using calcium channel blockers.

Limitations

This study has several important limitations. First, the AFFIRM trial was not designed as a trial comparing calcium channel blockers versus beta-blockers and this subanalysis was not prespecified in the study protocol. Due to the non-randomised nature, there is a risk of residual confounding despite adjusting for baseline characteristics. Therefore, no definite conclusions about drug differences with respect to causing significant bradycardias can be drawn. Second, some patients were excluded from this analysis because data on baseline rate control drugs were missing. The risk of selection bias should be taken into consideration. Third, there is no information about the dosages of rate control drugs or changes in dosages during the trial. Fourth, there was no linked data available on bradycardia and complications such as syncope or need for pacemaker implantations. Therefore, no statements can be made about symptomatology of bradycardias. Lastly, information of types of beta-blockers used was not available. These results must be seen as hypothesis generating only.

Conclusion

In patients with non-permanent AF included in the AFFIRM trial, calcium channel blockers instituted for rate control were associated with less bradycardia during sinus rhythm compared with beta-blockers. There were no differences in achieving resting heart rates <110 bpm during AF between patients treated with calcium channel blockers and beta-blockers.

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Contributors TK was involved in the study design, data acquisition, conducted the statistical analyses and wrote the manuscript. MR and RGT were involved with the study design, data acquisition and interpretation of results and critically reviewed the manuscript. IVG and HJGMC were involved in the interpretation of the data and critically reviewed the manuscript. All authors approved the final version. RGT is the guarantor of this manuscript.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The institutional review boards of the University of Washington and each of the 213 individual clinical sites and their satellite sites approved of the protocol (PMID: 12466506). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. This manuscript was prepared using AFFIRM research data obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Centre.

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