

# Rate control drugs differ in the prevention of progression of atrial fibrillation

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Received 12 January 2021; editorial decision 29 June 2021; accepted after revision 14 July 2021; online publish-ahead-of-print 20 August 2021

## Aims

We hypothesize that in patients with paroxysmal atrial fibrillation (AF), verapamil is associated with lower AF progression compared to beta blockers or no rate control.

## Methods and results

In this pre-specified *post hoc* analysis of the RACE 4 randomized trial, the effect of rate control medication on AF progression in paroxysmal AF was analysed. Patients using Vaughan-Williams Class I or III antiarrhythmic drugs were excluded. The primary outcome was a composite of first electrical cardioversion (ECV), chemical cardioversion (CCV), or atrial ablation. Event rates are displayed using Kaplan–Meier curves and multivariable Cox regression analyses are used to adjust for baseline differences. Out of 666 patients with paroxysmal AF, 47 used verapamil, 383 used beta blockers, and 236 did not use rate control drugs. The verapamil group was significantly younger than the beta blocker group and contained more men than the no rate control group. Over a mean follow-up of 37 months, the primary outcome occurred in 17% in the verapamil group, 33% in the beta blocker group, and 33% in the no rate control group ( $P=0.038$ ). After adjusting for baseline characteristics, patients using verapamil have a significantly lower chance of receiving ECV, CCV, or atrial ablation compared to patients using beta blockers [hazard ratio (HR) 0.40, 95% confidence interval (CI) 0.19–0.83] and no rate control (HR 0.64, 95% CI 0.44–0.93).

## Conclusion

In patients with newly diagnosed paroxysmal AF, verapamil was associated with less AF progression, as compared to beta blockers and no rate control.

## Keywords

Atrial fibrillation • Atrial fibrillation progression • Rate control • Rhythm control • RACE 4 study

## Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia, with a lifetime risk of 23%.<sup>1,2</sup> Atrial fibrillation has a tendency to progress to

more persistent forms over time.<sup>3</sup> Progression from paroxysmal AF to persistent or permanent AF is associated with increased disease burden, and hospitalization rates.<sup>4</sup> Progression of AF might be related

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## What's new

- Patients using verapamil demonstrate significantly less progression of atrial fibrillation (AF) than patients using beta blockers or no rate control medication.
- Patients using verapamil require fewer electrical cardioversions compared to patients using beta blockers and no rate control.
- There is no difference in progression of AF between patients using beta blockers or no rate control.

to structural and electrical remodelling of the atria.<sup>5–7</sup> There is growing evidence that continued calcium influx during rapid atrial rates plays a major role in electrical remodelling.<sup>8</sup> Several studies have shown that non-dihydropyridine calcium channel antagonists (CCA), such as verapamil, reduce tachycardia-induced electrical remodelling in AF.<sup>9–12</sup> Furthermore, in contrast to beta blockers, verapamil increases sympathetic tone.<sup>13</sup> In patients with vagal paroxysmal AF, verapamil has shown to reduce progression to persistent AF compared to digoxin and beta blockers.<sup>14</sup> Considering the above effects, rate control with non-dihydropyridine CCA in the general AF population may reduce progression of AF.

We investigated this hypothesis in paroxysmal AF patients who were included in the RACE 4 trial.<sup>15</sup> We identified patients with paroxysmal AF using verapamil, beta blockers, or no rate control medication at their first outpatient visit and compared their effect on AF progression. For the purpose of the present analysis, AF progression was defined as the need for atrial ablation, electrical cardioversion (ECV), or chemical cardioversion (CCV), all an expression of progressive symptoms as well as AF persistence.

## Methods

The RACE 4 trial is a multi-centre study in which nurse-led AF care was compared to routine care. A detailed description of the methods, intervention, and follow-up has been described by Petra Wjtvliet *et al.*<sup>15</sup> In short, 1375 AF patients were enrolled in the study in 8 hospitals in the Netherlands, from 2012 through 2017. Inclusion criteria were  $\geq 18$  years of age and presenting with first detected AF. Patients with unstable heart failure or acute coronary disease in the 3 months prior to screening were excluded. The patients were randomized to either nurse-led care or routine care.

For the present study, we selected all patients with paroxysmal AF, and classified them according to treatment with a beta blocker, verapamil, or no rate control medication. Patients using Class I or Class III antiarrhythmic drugs, including sotalol, were excluded. Patients were divided into a verapamil group, a beta blocker group, and a no rate control group based on their discharge medication after the first outpatient clinic visit. The primary outcome of this study was the occurrence of first ECV, CCV, or atrial ablation whichever came first. The secondary outcomes were the individual components of the primary outcome and a composite of cardiovascular death, hospital admission for arrhythmias, heart failure, thromboembolic events, major bleeding, acute coronary syndrome, or life-threatening effects of drugs. In RACE 4, patients had a maximum follow-up of 5 years and 10 months.

## Statistical analysis

Normally distributed variables are reported as mean  $\pm$  standard deviation, non-normally distributed variables as median (25–75% range), and categorical variables as count (percentage of patients). Differences between variables were tested using one-way ANOVA for normally distributed variables and Kruskal–Wallis for non-normally distributed variables. The Fisher's exact test was used to test for differences between categorical variables. Cumulative incidences over time were displayed using Kaplan–Meier curve, the *P*-value for between-group differences was calculated using the log rank test. Multivariable Cox regression analysis was performed to adjust for differences in baseline characteristics. The proportional hazard assumptions for this model were tested. The characteristics used for this analysis were the individual parameters used in the HATCH score:<sup>4</sup> age, heart failure, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and a history of a stroke in addition to sex and the presence of symptoms at first presentation. All tests performed were two-sided. Overall a *P*-value  $< 0.05$  was considered to be statistically significant. Bonferroni correction was used to correct for multiple testing in *post hoc* analysis. Data analysis was performed using R statistics (version 4.0.0).

## Results

### Baseline characteristics

A total of 666 patients with paroxysmal AF without Class I or Class III antiarrhythmic medication were included in the present analysis. Forty-seven patients used verapamil at baseline, 383 patients used beta blockers, and 236 patients used no rate control. The verapamil group was significantly younger than the beta blocker group and contained fewer men than the no rate control group (Table 1). Patients in the verapamil and the no rate control groups used fewer oral anticoagulation drugs compared to the beta blocker groups. There were no other differences in co-medication. At baseline, patients in the verapamil group had slightly higher heart rates, less often heart failure and a lower HATCH score compared to the other two groups. These differences were not significant.

### Primary outcome

Over a mean follow-up of 37 months, the primary outcome occurred in 8 out of 47 patients (17%) in the verapamil group, 126 out of 383 patients (33%) in the beta blocker group, and 78 out of 236 patients (33%) in the no rate control group ( $P = 0.038$ , Figure 1A). After adjusting for baseline characteristics, patients in the verapamil group had a significantly lower chance of receiving ECV, CCV, or atrial ablation compared to patients in the beta blocker group [hazard ratio (HR) 0.40, 95% confidence interval (CI) 0.19–0.83] and no rate control (HR 0.64, 95% CI 0.44–0.93).

### Secondary outcomes

When ECV, CCV, and ablation are analysed separately, patients using verapamil had a significantly lower probability of requiring an ECV ( $P = 0.021$ , Figure 1B). Electrical cardioversion was performed in 4 of 47 (9%) patients in the verapamil group, 95 of 383 (25%) patients in the beta blocker group, and 50 of 236 (21%) in the no rate control group. When adjusted for baseline characteristics, patients in the verapamil group had a significantly lower probability of requiring ECV

**Table 1** Characteristics of the patients at baseline

	Verapamil (n = 47)	Beta blocker (n = 383)	No rate control (n = 236)	P-value
Age (years)	60 (55–68) <sup>a</sup>	66 (59–72) <sup>b</sup>	63 (55–69)	<0.01
Male sex, n (%)	23 (49)	234 (61) <sup>b</sup>	170 (72) <sup>c</sup>	<0.01
Symptoms at first visit, n (%)	22 (47)	178 (46)	91 (39)	0.141
Heart rate at first visit (beats per minute)	76 (65–91)	71 (61–94)	73 (65–91)	0.75
Hypertension, n (%)	20 (43)	198 (52) <sup>b</sup>	89 (38)	<0.01
History of heart failure, n (%)	1 (2)	37 (9)	11 (5)	0.03
Diabetes, n (%)	2 (4)	41 (11)	18 (8)	0.25
Ischaemic stroke or transient ischaemic attack, n (%)	2 (4)	27 (7)	14 (6)	0.76
Haemorrhagic stroke, n (%)	0 (0)	7 (2)	5 (2)	1
Coronary artery disease, n (%)	3 (6)	28 (7)	9 (4)	1
Valvular heart disease, n (%)	1 (2)	18 (5)	6 (3)	0.37
Peripheral vascular disease, n (%)	1 (2)	13 (3)	8 (3)	1
Hyperthyroidism, n (%)	0 (0)	8 (2)	1 (0)	0.27
Chronic obstructive pulmonary disease, n (%)	5 (11)	22 (6)	9 (4)	0.13
CHA2DS2-VASc, <sup>d</sup> n (%)				<0.01
0	18 (38)	80 (21)	83 (35)	
1	9 (19)	68 (18)	48 (20)	
≥2	20 (42)	235 (61)	105 (44)	
HATCH score, <sup>e</sup> n (%)				<0.01
0	24 (51)	142 (37)	128 (54)	
1	19 (40)	154 (40)	79 (33)	
≥2	4 (9)	87 (23)	29 (12)	
HASBLED >3, n (%)	5 (11)	37 (10)	16 (7)	0.36
Body mass index (kg/m <sup>2</sup> )	28 (±5)	28 (±5)	27 (±5)	0.58
Systolic blood pressure (mmHg)	141 (±20)	141 (±21)	141 (±19)	0.98
Echocardiographic left atrial size, long axis (mm)	38 (±5)	39 (±6)	39 (±6)	0.30
Left ventricular ejection fraction (%)	60 (55–60)	55 (52–60)	57 (55–60)	0.06
RAAS inhibition, n (%)	7 (15)	79 (21)	39 (17)	0.35
ACE inhibitor	4 (9)	61 (16)	25 (11)	0.10
Angiotensin receptor blocker	3 (6)	18 (5)	14 (6)	0.67
Dihydropyridine calcium channel blockers, n (%)	1 (2)	23 (6)	10 (4)	0.497
Diuretics, n (%)	3 (6)	40 (10)	14 (6)	0.14
Statins, n (%)	5 (11)	50 (13) <sup>b</sup>	14 (6)	0.01
Digoxin, n (%)	1 (2)	16 (4) <sup>b</sup>	0 (0)	<0.01
Oral anticoagulation, n (%)	26 (55) <sup>a</sup>	289 (75) <sup>b</sup>	119 (50)	<0.01
Direct oral anticoagulation, n (%)	18 (38)	169 (44)	63 (27)	
Coumarines, n (%)	8 (17)	120 (31)	56 (24)	

ACE, angiotensin-converting enzyme; RAAS, renin–angiotensin–aldosterone system.

Significant differences between groups after correction for multiple testing using the Bonferroni correction.

<sup>a</sup>Significant difference between verapamil and beta blocker.

<sup>b</sup>Significant difference between beta blocker and no rate control.

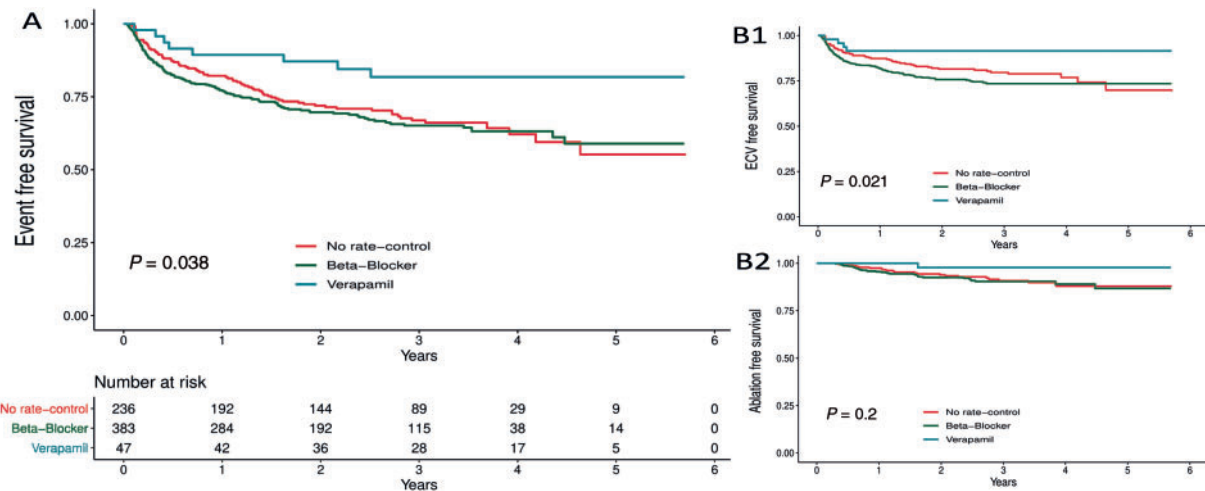
<sup>c</sup>Significant difference between no rate control and verapamil.

<sup>d</sup>Congestive heart failure, hypertension, an age of 65–74 years, diabetes, and vascular disease are each assigned one point, and previous stroke or transient ischaemic attack and an age >75 years are assigned two points.

<sup>e</sup>Age above 75 years, hypertension and chronic obstructive pulmonary disease are each assigned one point and heart failure and previous stroke or transient ischaemic attack are each assigned two points.

compared to the beta blocker group (HR 0.31, 95% CI 0.11–0.85) and the no rate control group (HR 0.59, 95% CI 0.35–1.00). ECV or CCV, whichever came first, was performed in 189 (28%) out of 666 patients overall. There was no difference in ECV and CCV free overall survival (Supplementary material online, Figure S1). But similar to ECV alone, when adjusted for baseline characteristics, the verapamil group had a significantly lower probability of receiving ECV or CCV compared to

the beta blocker group (HR 0.41, 95% CI 0.19–0.89) and the no rate control group (HR 0.65, 95% CI 0.44–0.97). In total, 56 (8%) atrial ablations were performed, 1 (2%) was performed in the verapamil group, 34 (9%) were performed in the beta blocker group, and 21 (9%) were performed in the no rate control group. There were no significant differences in atrial ablations performed between groups ( $P=0.20$ , Figure 1B) even when adjusted for baseline characteristics (Table 2). We



**Figure 1** Rate control medication and event free survival from (A) ECV-CCV-Ablation, (B1) ECV and (B2) ablation.

**Table 2** Cox regression analysis of the effect of different rate control drugs

	Hazard ratio	95% confidence interval
Composite outcome		
Verapamil vs. beta blockers	0.4	0.19–0.83
Verapamil vs. no rate control	0.64	0.44–0.93
Beta blocker vs. no rate control	1.09	0.81–1.47
ECV		
Verapamil vs. beta blockers	0.31	0.11–0.85
Verapamil vs. no rate control	0.59	0.35–1.00
Beta blocker vs. no rate control	1.32	0.92–1.90
ECV and CCV		
Verapamil vs. beta blockers	0.41	0.19–0.89
Verapamil vs. no rate control	0.65	0.44–0.97
Beta blocker vs. no rate control	1.1	0.81–1.52
Atrial ablation		
Verapamil vs. beta blockers	0.18	0.02–1.33
Verapamil vs. no rate control	0.46	0.17–1.28
Beta blocker vs. no rate control	1.18	0.67–2.10

Adjusted for the individual components of HATCH score: age, heart failure, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and a history of a stroke in addition to sex and presents of symptoms at first presentation.

CCV, chemical cardioversion; ECV, electrical cardioversion.

performed a sensitivity analysis excluding the patients who underwent ablation. This did not change the results on AF progression as expressed by ECV and CCV free survival (data not shown).

The secondary composite outcome of cardiovascular death, hospital admission for arrhythmias, heart failure, thromboembolic events, major bleeding, acute coronary syndrome, or life-threatening effects of drugs occurred in 11 patients (23%) in the verapamil group, 113 (30%) in the beta blocker group, and 62 (26%) times in the no rate control group, this was not significantly different ( $P=0.52$ , Table 3). The secondary outcome was mostly driven by hospital admissions for arrhythmic events which occurred in 8 patients (17%) in the

verapamil group, 82 patients (24%) in the beta blocker group, and 56 patients (24%) in the no rate control group ( $P=0.61$ ). There were also no significant differences between any of the other components of the composite secondary outcome. For a full overview of the secondary outcome see Table 3.

## Discussion

This pre-defined *post hoc* analysis from the RACE 4 trial suggests that in patients with newly diagnosed paroxysmal AF verapamil may reduce the progression to persistent AF.

**Table 3** Secondary outcomes

	Verapamil (n = 47)	Beta blocker (n = 383)	No rate control (n = 236)	P-value
Composite of secondary outcome, n (%)	11 (23)	113 (30)	62 (26)	0.52
Cardiovascular death, n (%)				
Cardiac	0 (0)	0 (0)	0 (0)	1
Vascular non-cardiac	1 (2)	2 (1)	1 (0)	0.27
Hospitalizations for arrhythmic events, n (%)	8 (17)	92 (24)	56 (24)	0.61
Heart failure, n (%)	1 (2)	7 (2)	5 (2)	0.91
Acute coronary syndrome, n (%)	0 (0)	6 (2)	3 (1)	1
Ischaemic thromboembolic complications, n (%)	1 (2)	10 (3)	1 (0)	0.1
Major bleeding, n (%)	0 (0)	9 (2)	3 (1)	0.57
Life-threatening effects of drugs, n (%)	1 (2)	2 (1)	0 (0)	0.155

These results are in agreement with earlier findings in the EURO Heart Survey, where it was demonstrated that in patients with vagal AF, verapamil reduced the progression to persistent AF, compared to digoxin or beta blocker treated patients.<sup>14</sup> Even in patients with persistent AF requiring ECV, verapamil showed an increase in spontaneous conversion to sinus rhythm and reduced the amount of ECV's required to achieve sinus rhythm compared to digoxin.<sup>16</sup> Furthermore, supplementing Class 1C and Class III antiarrhythmic drug therapy with verapamil reduced AF recurrences after ECV.<sup>17</sup> These results could be due to the electrophysiological effects of verapamil. Rapid atrial rates lead to calcium loading in the sarcoplasmic reticulum and increased calcium leakage from the sarcoplasmic reticulum. This calcium leak from the sarcoplasmic reticulum promotes cellular arrhythmogenesis in paroxysmal AF patients by inducing delayed afterdepolarization and triggered activity.<sup>18</sup> Furthermore, calcium-handling abnormalities may play a role in AF perpetuation through conduction slowing and shortening of the refractory period, thereby promoting re-entry.<sup>12</sup> In several animal studies, verapamil has been shown to prevent electrical remodelling and reduce shortening of the refractory period during rapid atrial rates.<sup>11,19</sup> This effect is particularly strong early after onset of rapid atrial rates and may dissipate after long periods of rapid atrial rates.<sup>20</sup> This may explain why in our patients with paroxysmal AF, verapamil was associated with less arrhythmia progression, whereas this was less clear in patients with persistent AF.<sup>16,21</sup> By increasing triggers and promoting re-entry, calcium-handling abnormalities could play a major role in the progression of AF. The decrease in AF progression in the verapamil group might be explained by verapamil preventing or delaying electrical remodelling. In contrast, digoxin has been shown to decrease recovery from electrical remodelling.<sup>22</sup> However, since concomitant use of digoxin was low and equally distributed among the groups, it is unlikely that digoxin use contributed to the results of the present analysis.

On the other hand, the result could also be explained by verapamil being superior for rate control,<sup>23,24</sup> especially in patients with paroxysmal AF, thereby reducing symptoms and the need for a cardioversion or ablation. This can be explained by the fact that verapamil specifically lowers the heart rate during AF, but not during sinus rhythm. In contrast, the dose of beta blockers and their rate controlling effect during paroxysms of AF is limited by the heart rate during sinus rhythm. Therefore, heart rate during AF episodes in the beta blocker patients may have been more rapid, with the risk of

ventricular dysfunction and subsequent atrial structural remodelling and AF progression.<sup>22</sup> Furthermore, lower heart rates during sinus rhythm can promote atrial extra systoles, potentially triggering AF.

The patients receiving verapamil in this analysis were generally younger and had fewer comorbidities that are known to increase AF progression and disease burden, such as hypertension, history of heart failure, diabetes mellitus, and a previous stroke.<sup>4</sup> It has been confirmed that targeted treatment of these comorbidities improves sinus rhythm maintenance,<sup>25</sup> and therefore it has received a prominent place in the ESC guidelines.<sup>26</sup> The differences in comorbidities could, in part, be responsible for differences in AF progression. Even after statistically adjusting for these comorbidities, residual confounding could still be present. These results justify further study of the effects of verapamil on AF progression in patients with paroxysmal AF with a randomized controlled trial.

## Limitations

In the RACE 4 trial rate control treatment was not randomized, so no statements can be made about causality between rate control strategy and symptomatology or AF progression. Due to the different contraindications and side effects of verapamil and beta blockers there is the possibility of confounding factors or residual confounding after adjusting for baseline characteristics. The verapamil group is also much smaller than the beta blocker and the no rate control groups, therefore these data cannot be extrapolated to clinical practice and should be seen as hypotheses generating. Since medication persistence was no objective of the RACE 4 trial, we could not adjust for this factor.

Due to low event rates, the present analysis was underpowered for some of the study outcomes, mainly atrial ablation, heart failure, or death, which have a low incidence overall.

## Conclusion

In patients with newly diagnosed paroxysmal AF, verapamil was associated with less AF progression, as compared to beta blockers and no rate control medication.

## Funding

This research was supported by Netherlands healthcare insurance companies (DSW, ACHMEA, and CZ), Boehringer Ingelheim, Bayer, Pfizer, Bristol-Myers Squibb, and Daiichi Sankyo.

**Conflict of interest:** R.G.T. reports grants and personal fees from Boehringer Ingelheim, Bristol-Meyers-Squibb, Pfizer, and Daiichi Sankyo and grants from Bayer during the conduct of the study. N.A.H.A.P. reports grants from Boehringer Ingelheim, Medtronic, Bayer, Pfizer, Bristol-Myers-Squibb, and Daiichi Sankyo and grants from Netherlands Health Insurance companies DSW, ACHMEA, and CZ, during the conduct of the study, all to the institution. M.R. reports grants from Netherlands Cardiovascular Research Initiative funded by Dutch Heart Foundation, outside the submitted work. J.G.L.M.L. reports grants from the Netherlands Cardiovascular Research Initiative funded by the Dutch Heart Foundation, grants from Boehringer Ingelheim, Medtronic, Abbott, Bayer, Pfizer, Bristol-Myers Squibb, Daiichi Sankyo, and Biotronik, and grants from the Netherlands Health Insurance companies DSW, Achmea, and VGZ, all to the institution, and personal fees from Medtronic, outside the submitted work. H.J.G.M.C., I.C.V.G., and M.R. report grants from the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation, CVON 2014–9: Reappraisal of Atrial Fibrillation: interaction between hyperCoagulability, Electrical remodelling, and Vascular destabilization in the progression of AF (RACE V) outside the submitted work; and grants from Boehringer Ingelheim, Medtronic, Abbott, Bayer, Pfizer, Bristol-Myers-Squibb and Daiichi Sankyo, and from the Netherlands Health Insurance companies DSW, Achmea, and VGZ, during conduct of the study, and all to the institution. All other authors declared no conflict of interest.

## Data availability

The data underlying this article cannot be shared publicly due to privacy reasons of the participants. Researchers can request the data by submitting a reasonable proposal to the corresponding author.

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