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Optimal treatment of underlying conditions improves rhythm control outcome in atrial fibrillation – Data from RACE 3

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Abstract Atrial fibrillation (AF) is a progressive disease, and maintenance of sinus rhythm is cumbersome. In this analysis of the Routine versus Aggressive risk factor driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) trial we aimed to determine whether optimal treatment of underlying conditions of AF improves maintenance of sinus rhythm in patients with persistent AF and moderate heart failure (HF). Our data showed that optimal treatment of blood pressure, LDL-cholesterol and heart failure was associated with an increase in sinus rhythm maintenance compared to conventional therapy (87% versus 63%, $P = .002$, respectively). (Am Heart J 2020;226:235-39.)

Atrial fibrillation (AF) often causes symptoms, and has an increased risk of cardiovascular morbidity and death.¹ Maintaining sinus rhythm improves symptoms, but has also been associated with improved outcome in a selected group of patients, mainly patients with heart failure with a reduced ejection fraction.² The underlying diseases of AF, such as hypertension, but also the arrhythmia itself cause atrial remodeling which results in progression of AF.³ Optimal control of hypertension with angiotensin-converting enzyme inhibitors (ACE-inhibitors) and angiotensin II receptor blockers (ARBs) has been shown to have effect on incident AF and AF recurrences after ablation.^{4, 5} Further, it prevents cardiovascular morbidity and death.⁵

The aim of the Routine versus Aggressive risk factor driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) trial was to evaluate if targeted therapy of underlying conditions would improve risk factors of AF, and therefore would postpone atrial remodeling, and improve sinus rhythm maintenance.⁶ The study showed that targeted therapy of underlying conditions was associated with a reduction in body mass index (BMI), blood pressure, lipid levels and N-terminal pro-brain natriuretic peptide (NTproBNP). Furthermore, targeted therapy improved maintenance of sinus rhythm. However, optimal medical therapies were not achieved in all patients. We now hypothesize that optimal treatment of underlying conditions of AF further improves maintenance of sinus rhythm in patients with early persistent AF and heart failure (HF).

Methods

This analysis was performed in patients included in the RACE 3 study.⁶ In brief, the RACE 3 trial ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00877643) identifier NCT00877643) was a prospective, randomized,

multicenter, open-label trial in patients with early persistent AF and mild to moderate HF. Patients were randomized to targeted therapy of underlying conditions ($N = 119$) or conventional therapy ($N = 126$). Both groups received causal treatment of AF and HF, and rhythm control therapy, as in routine clinical practice, according to the guidelines. Electrical cardioversion (ECV) was scheduled 3 weeks after inclusion. If AF relapse occurred, repeat ECV, antiarrhythmic drugs and atrial ablations were allowed. In the intervention group, on top of that, four therapies were started: (1) mineralocorticoid receptor, (2) statins, (3) ACE-inhibitors and/or ARBs, and (4) cardiac rehabilitation including physical activity, dietary restrictions, and counseling. The primary endpoint was sinus rhythm at 1-year during 7 days of Holter monitoring. Targeted therapy was shown to be superior to conventional therapy in maintaining sinus rhythm with 75% maintaining sinus rhythm in the targeted group versus 63% in the conventional group ($P = .042$).

In this analysis, we compared patients with optimal treatment of the underlying conditions in the targeted group with patients included in the conventional group. Optimal treatment was defined as fulfillment of the following criteria at 1-year follow-up: (1) blood pressure $\leq 140/85$ mmHg, (2) LDL-cholesterol ≤ 3.00 mmol/L, and (3) absolute NTproBNP of <400 pg/mL, or decrease of $\geq 75\%$ if the patient was in sinus rhythm, or decrease of $\geq 20\%$ if in AF. Primary endpoint was sinus rhythm maintenance at 1-year follow-up. Secondary endpoints were changes in underlying conditions at 1-year follow-up.

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Results

A total of 194 patients were included in this analysis, 68 of 119 (57%) of the targeted and all conventional patients (N = 126). The targeted patients were only included when they met all optimal criteria. In the targeted group, 94 (79%) patients met the optimal blood pressure criteria, 100 (84%) the optimal LDL-cholesterol

criteria, and 91 (76%) the optimal NTproBNP criteria. This resulted in 68 of 119 patients (57%) meeting all optimal treatment criteria.

Baseline characteristics, apart from age, were comparable between the groups (Table I). Mean age was 64 ± 9 years, 79% were men, median AF history duration was 3 [interquartile range (IQR) 2–5] months, median HF history duration $2^{[1-4]}$ months, CHA₂DS₂-VASc score was 2.^[1-3] Hypertension was the most seen comorbidity.

At 1-year, sinus rhythm was present in 59 of 68 patients (87%) in the optimal group versus 79 of 126 patients (63%) in the conventional group (Figure 1A). Use of mineralocorticoid receptors (64 [94%] vs. 5 [4%]; $P < .001$), ACE-inhibitors and ARBs use (61 [90%] vs. 96 [76%]; $P = .049$),

Table I. Baseline characteristics

Characteristic	Total (n = 194)	Optimal treatment (n = 68)	Conventional therapy (n = 126)	P-value (between groups)
Age (years)	64 ± 9	62 ± 8	65 ± 9	0.020
Male sex	153 (79%)	54 (79%)	99 (79%)	1.000
Total duration AF (months)	3 (2–5)	3 (2–7)	3 (2–5)	0.364
Total persistent AF (months)	2 (1–4)	2 (1–3)	2 (1–4)	0.415
Duration HF (months)	2 (1–4)	2 (1–4)	2 (1–4)	0.973
Hospital admission for HF	30 (16%)	8 (12%)	22 (17%)	0.405
LVEF <45%	56 (29%)	19 (28%)	37 (29%)	0.870
Hypertension	114 (59%)	36 (53%)	78 (62%)	0.285
Diabetes	20 (10%)	4 (6%)	16 (13%)	0.215
Coronary artery disease	23 (12%)	9 (13%)	14 (11%)	0.649
Ischemic thromboembolic complication	8 (4%)	4 (6%)	4 (3%)	0.454
Chronic obstructive pulmonary disease	16 (8%)	5 (7%)	11 (9%)	1.000
CHA ₂ DS ₂ -VASc score *	2 (1–3)	2 (1–2)	2 (1–3)	0.053
Body mass index (kg/m ²)	29 (26–31)	29 (26–31)	28 (25–31)	0.325
Blood pressure (mmHg)				
Systolic	129 ± 15	129 ± 15	128 ± 15	0.895
Diastolic	82 ± 10	83 ± 10	82 ± 10	0.225
Heart rate at rest in AF (bpm)	87 (78–99)	86 (76–96)	88 (78–100)	0.382
NYHA classification				0.853
I	37 (19%)	13 (19%)	24 (19%)	
II	133 (69%)	48 (71%)	85 (67%)	
III	24 (12%)	7 (10%)	17 (13%)	
EHRA classification	2 (2–2)	2 (2–2)	2 (2–2)	0.713
NT-pro BNP (pg/mL)	1051 (705–1645)	1071 (700–1487)	1039 (717–1755)	0.498
Medications				
Beta-blocker	168 (87%)	60 (88%)	108 (86%)	0.824
Verapamil/ diltiazem	11 (6%)	0 (0%)	11 (9%)	0.009
Digoxin	49 (25%)	17 (25%)	32 (26%)	1.000
ACE-inhibitor	70 (36%)	22 (32%)	48 (38%)	0.436
Angiotensin receptor blocker	42 (22%)	14 (21%)	28 (22%)	0.856
Mineralocorticoid Receptor Antagonist	4 (2%)	1 (1%)	3 (2%)	1.000
Statin	64 (33%)	22 (32%)	42 (34%)	1.000
Diuretic	75 (39%)	27 (40%)	48 (38%)	0.878
Anticoagulant	190 (98%)	66 (97%)	124 (98%)	0.284
Echocardiographic variables				
Left atrial size, long axis (mm)	43 (39–47)	43 (40–47)	44 (39–47)	0.810
Left atrial volume index (mL/m ²)	37 (31–48)	37 (30–45)	38 (32–47)	0.562
LV ejection fraction (%)	50 (43–59)	50 (42–56)	50 (43–60)	0.521

Data are mean (SD), number of patients (%), or median (IQR).

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; EHRA, European Heart Rhythm Association class for symptoms; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

* The CHA₂DS₂-VASc score assesses thromboembolic risk. C = congestive heart failure/LV dysfunction, H = hypertension; A₂ = age ≥ 75 years; D = diabetes mellitus; S₂ = stroke/transient ischemic attack/systemic embolism; V = vascular disease; A = age 65–74 years; Sc = (sex category (female sex)).

Figure 1

Outcome at 1-year follow-up A: Sinus rhythm maintenance on 7-day Holter monitoring. B: Intervention medication at 1-year follow-up. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

and statins (66 [97%] vs. 61 [48%]; $P < .001$) was significantly different between the optimal and the conventional group at 1-year (Figure 1B). The number of patients with repeat ECV (32 [47%] vs. 64 [51%]; $P = .654$), total number of ECVs during the first 6 months (35 vs. 75; $P = .486$), and last 6 months (17 vs. 18; $P = .112$), institution of any antiarrhythmic drug (31 [46%] vs. 54 [43%]; $P = .763$), sotalolol (11 [16%] vs. 16 [13%]; $P = .520$), amiodarone (17 [25%] vs. 31 [25%]; $P = 1.000$), flecainide (9 [13%] vs. 9 [7%]; $P = .197$), and dronedarone use (0 [0%] vs. 2 [2%]; $P = .542$), as well as atrial ablations (1 [2%] vs. 2 [2%]; $P = 1.000$) were comparable.

At 1-year significant changes were seen in blood pressure, BMI, NTproBNP and cholesterol levels, in favor of the optimal group (Table II). No differences were seen in left atrial volume and left ventricular ejection fraction (LVEF).

Analyses comparing both groups matched for age showed comparable results (Supplementary Table 1, Supplementary Table 2, and Supplementary Figure). In an additional analysis we compared maintenance of sinus rhythm in all optimally treated patients in both groups versus the non-optimally treated patients. Sinus rhythm was present in 81 of 92 (88%) versus 87 of 153 (57%) patients, $P < .001$, respectively (Supplementary Table 3).

Discussion

Our data shows that optimal treatment of underlying conditions can increase sinus rhythm maintenance by 24% compared to conventional therapy. In comparison,

with the overall RACE 3 the difference between the targeted (75%) and conventional group (63%), was 12%.

Moreover, patients from the targeted and conventional group that were optimally treated for underlying conditions showed significantly better sinus rhythm maintenance rate than patients who were not optimally treated, independent of which randomization group patients were in. These findings are in line with previous data showing that in obese patients aggressive treatment of underlying conditions reduced the severity of the underlying diseases and in association with that improved sinus rhythm maintenance.⁴ Furthermore, several studies showed the beneficial effects of renin-angiotensin-aldosterone blockers for prevention of (incident) AF. ACE-inhibitors and ARBs were effective for the prevention of incident AF in patients with systolic left ventricular dysfunction or left ventricular hypertrophy.⁵ ARBs in combination with amiodarone reduced the recurrence rate of AF more than when AF was only treated with amiodarone. Eplerenone reduced the incidence of AF in patients with heart failure with a reduced ejection fraction.⁷ Statins may have contributed due to their anti-inflammatory effects.⁸

The mechanisms why ACE-inhibitors, ARBs, statins and mineralocorticoid receptors have beneficial effects on reduction of AF incidence and burden are not totally clear yet but are probably twofold. First, these medications improve the underlying conditions, i.e. the improvement of hypertension and the hemodynamic situations in patients with heart failure. Additionally, they may reduce the process of remodeling by reducing fibrosis and inflammation.⁷

Table II. Changes in underlying conditions.

Characteristic	Optimal Treatment (n = 68)	Conventional therapy (n = 126)	Δ Optimal Treatment (baseline vs. 1- year) %	Δ Conventional therapy (baseline vs. 1-year) %	P-value optimal treatment baseline vs. 1- year	P-value conventional treatment baseline vs. 1- year	P-value Δ Optimal vs. Conventional
Systolic blood pressure (mmHg)							
Baseline	128.5 ± 15.3	128.2 ± 14.5	-5.11%	2.05%	<0.001	0.228	0.001
1-year	120.8 ± 12.4	129.6 ± 16.1					
Diastolic blood pressure (mmHg)							
Baseline	83.5 ± 10.4	81.6 ± 9.9	-11.37%	-2.31%	<0.001	0.006	<0.001
1-year	73.2 ± 8.0	78.8 ± 9.9					
Body mass index (kg/m ²)							
Baseline	29.1 (25.4–31.2)	28.1 (25.4–31.1)	-0.61%	1.37%	0.720	0.002	0.040
1-year	28.7 (26.1–31.2)	28.1 (26.1–31.5)					
NT-ProBNP (ng/L)							
Screening	1070.6 (698.6– 1500.3)	1039.2 (717.0– 1754.8)	-83.36%	-37.26%	<0.001	<0.001	<0.001
Month 12	135.8 (68.8– 235.4)	257.5 (130.5– 924.5)					
Total Cholesterol (mmol/l)							
Baseline	4.8 (4.1–5.7)	5.0 (4.1–4.8)	-15.81%	1.65%	<0.001	0.971	<0.001
1-year	4.0 (3.5–4.5)	4.9 (4.2–5.7)					
LDL Cholesterol (mmol/l)							
Baseline	3.0 (2.4–3.8)	2.9 (2.5–3.8)	-20.83%	0.40%	<0.001	0.440	<0.001
1-year	2.1 (1.8–2.5)	2.9 (2.3–3.7)					
LA volume index (ml/m ²)							
Baseline	36.6 (30.0–46.9)	37.6 (32.1–47.6)	-4.93%	2.40%	0.033	0.100	0.299
1-year	34.0 (28.6–38.9)	35.6 (27.3–45.0)					
LVEF							
Baseline	50 (48–57)	51 (43–60)	21.53%	15.67%	<0.001	<0.001	0.185
1-year	58 (55–60)	56 (52–60)					
Septal thickness (mm)							
Baseline	10 (9–11)	10 (9–11)	4.42%	0.95%	0.484	0.546	0.447
1-year	10 (9–11)	10 (9–11)					
Posterior thickness (mm)							
Baseline	10 (9–10)	10 (9–11)	0.28%	-0.13%	0.496	0.226	0.994
1-year	10 (9–11)	9 (8–11)					

Data are mean (SD), number of patients (%), or median (IQR).

NT-proBNP, N-terminal pro-brain natriuretic peptide; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction.

In terms of blood pressure lowering our results are in contrast to the study of Parkash et al.⁹ This might be due to differences in study population. Our population consisted of patients with moderate heart failure. Further, it is well known that even borderline increased blood pressure is associated with an increased risk of incident AF and that aggressive treatment of lowering blood pressure is associated with a better prognosis.^{10, 11} Finally, our treatment included more than targeting blood pressure.

At 1-year follow-up LVEF was not different between the groups, but NTproBNP was. In the present study

predominantly patients with heart failure with a preserved ejection fraction (HFpEF) were included. At baseline, NTproBNP was assessed while patients were in AF. At 1-year follow-up, the reduction in NT-proBNP is probably related to both the presence of sinus rhythm in the majority of patients and better treatment of heart failure, in the setting of HFpEF.

Age is an important risk factor for AF. Therefore we performed an aged matched comparison which revealed also a significant higher percentage of sinus rhythm maintenance in favor of the optimal treatment group.

Limitations

Per criteria a decent percentage of patients met the criteria. However, the patients who met all optimal treatments were lower than expected. As well known, the blood pressure target was difficult to achieve which may be associated with the occurrence of side effects and resistance to uptitrate dosages.¹² In addition, blood pressure measurement was limited to one assessment per visit; no 24-hour blood pressure measurement was done.

Conclusion

The present findings again stresses that early treatment of the underlying conditions has important potential to contribute to the success of rhythm control therapy in patients with persistent AF and moderate HF.

Appendix. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ahj.2019.12.005>.

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