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Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial

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Aims Atrial fibrillation (AF) is a progressive disease. Targeted therapy of underlying conditions refers to interventions aiming to modify risk factors in order to prevent AF. We hypothesised that targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent AF.

Methods and results We randomized patients with early persistent AF and mild-to-moderate heart failure (HF) to targeted therapy of underlying conditions or conventional therapy. Both groups received causal treatment of AF and HF, and rhythm control therapy. In the intervention group, on top of that, four therapies were started: (i) mineralocorticoid receptor antagonists (MRAs), (ii) statins, (iii) angiotensin converting enzyme inhibitors and/or receptor blockers, and (iv) cardiac rehabilitation including physical activity, dietary restrictions, and counselling. The primary endpoint was sinus rhythm at 1 year during 7 days of Holter monitoring. Of 245 patients, 119 were randomized to targeted and 126 to conventional therapy. The intervention led to a contrast in MRA (101 [85%] vs. 5 [4%] patients, $P < 0.001$) and statin use (111 [93%] vs. 61 [48%], $P < 0.001$). Angiotensin converting enzyme inhibitors/angiotensin receptor blockers were not different. Cardiac rehabilitation was completed in 109 (92%) patients. Underlying conditions were more successfully treated in the intervention group. At 1 year, sinus rhythm was present in 89 (75%) patients in the intervention vs. 79 (63%) in the conventional group (odds ratio 1.765, lower limit of 95% confidence interval 1.021, $P = 0.042$).

Conclusions RACE 3 confirms that targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent AF.

Trial Registration number Clinicaltrials.gov NCT00877643.

Keywords Atrial fibrillation • Rhythm control • Risk factor management • Underlying conditions

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Introduction

Atrial fibrillation (AF), especially in combination with heart failure (HF), is associated with cardiovascular morbidity and mortality, with an increasing risk as AF progresses.[1,2] Maintenance of sinus rhythm marks an improved prognosis.[3] Due to its progressive nature,[4,5] long-term maintenance of sinus rhythm is cumbersome even when treating patients with ablation.[6] Atrial fibrillation progression is caused by atrial structural remodelling due to underlying conditions and AF itself.[4,5] Atrial remodelling is induced by activation of various pathways including activation of the renin–angiotensin–aldosterone system and inflammation, leading to enlarged atria and fibrosis.[4,7] Recognition of the consequences of atrial remodelling has led to the notion of intervening early in patients with AF in an attempt to improve sinus rhythm maintenance and AF associated complications.[5,8]

Cardiovascular risk reduction nowadays is crucial in AF management.[6] It improves outcome in patients who are comparable to AF populations.[9] A strategy that targets underlying conditions refers to interventions that aim to reduce cardiovascular risk and, in turn, reduce the atrial substrate in order to prevent incidence and progression of AF. It comprises treatment with drugs and strategies that affect the underlying conditions, and thus the causal pathophysiological atrial remodelling processes itself, in contrast to conventional antiarrhythmic drugs that affect conduction velocity and repolarisation. Therapies include angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) instituted for hypertension and HF, mineralocorticoid receptor antagonists (MRAs) for HF, statins for prevention of coronary and vascular events, and lifestyle management.[7,9–18] In addition, these interventions may favourably affect the atrial remodelling processes.

Therefore, we conducted a multicentre, randomized trial to test the hypothesis that targeted therapy of underlying conditions is of added value to conventional therapy for sinus rhythm maintenance in patients with early persistent AF and early HF.

Methods

Study design

The Routine vs. Aggressive risk factor driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) trial was a prospective, multicentre, randomized, open-label blinded endpoint trial designed to show superiority of targeted therapy of underlying conditions over conventional therapy in patients with early persistent AF and HF. The trial was investigator initiated. The patients were enrolled between May 2009 and November 2015 in 14 centres in The Netherlands and 3 in the UK (Supplementary material online, p. 2). The detailed design has been reported previously and is provided in the Supplementary material online (pp. 6–43).[19] Briefly, patients were enrolled if they had early symptomatic persistent AF [total AF history < 5 years, total persistent AF duration > 7 days but <6 months, ≤1 electrical cardioversion (ECV)], and early (total history < 1 year) HF with a preserved ejection fraction (HFpEF) or HF with a reduced ejection fraction (HFrEF). HFpEF was defined as left ventricular ejection fraction (LVEF) ≥45%, New York Heart Association (NYHA) functional Class II–III, and additional criteria consisting of echo parameters and/or elevated N-terminal pro-brain natriuretic peptide (NT-proBNP). HFrEF was defined as LVEF <45% and NYHA class I–III. Exclusion criteria included LVEF <25%, NYHA IV, left atrial size >50 mm, MRA use, and AF associated with surgery or acute illness. The study was done in compliance with the protocol and the ethics principles as outlined in the Declaration of Helsinki. The Institutional Review Board of all sites approved the protocol, and all participants gave written informed consent. All patients were randomly assigned in a 1:1 ratio to targeted or conventional therapy. Patients were stratified for LVEF < 45% and LVEF ≥ 45%.

Procedures

Both groups received causal treatment of AF and HF, [15] and were treated with rhythm control therapy.[6] Patients were scheduled for ECV 3 weeks after inclusion (Supplementary material online, *Figure S1*). If AF relapsed, repeat ECV, antiarrhythmic drugs and atrial ablations were allowed.[6]

In the targeted group, on top of that, four interventions were started: (i) MRA, (ii) statins, (iii) ACE-I and/or ARB, and (iv) cardiac rehabilitation, all according to our protocol (Supplementary material online, pp. 6–43). MRAs, ACE-Is, and ARBs were dosed aiming to achieve the highest tolerated doses. Blood pressure target was below 120/80 mmHg. Cardiac rehabilitation included physical activity, dietary restrictions, and scheduled counselling on drug adherence, exercise maintenance, and dietary restrictions every 6 weeks.[16] Patients received their first counselling visit 1 week after inclusion (i.e. 2 weeks before ECV), and every 6 weeks thereafter.

At baseline, clinical history, physical examination, current medication, an electrocardiogram, blood samples, 24-h urine collection, echocardiography, bicycle exercise test, and quality of life were assessed (Supplementary material online, *Figure A1*, p. 3). Outpatient clinic visits were scheduled at 1, 3, 6, 9, and 12 months after the first study ECV. Every 6 weeks, additionally, an electrocardiogram was recorded. After 1 year, 7-day Holter monitoring, 24-hour urine collection, echocardiography, exercise test, and quality of life were scheduled.

Outcomes

The primary endpoint required the presence of sinus rhythm, defined as sinus rhythm during at least six-seventh of assessable time, at the 7-day Holter monitoring at 1 year. If the 1-year Holter was not available, we used the best available clinical information for rhythm status as a proxy for the determination of the primary endpoint status. If the patient had died, the clinical and AF status before death were assessed (Supplementary material online, *Table A1*, p. 4).

The pre-specified secondary endpoints included number of ECVs, antiarrhythmic drugs, ablation, blood pressure, body mass index (BMI), NT-proBNP, cholesterol levels, sodium levels in 24-hour urine collection, left atrial volume, LVEF, hospitalizations, and all-cause mortality. An endpoint review committee, unaware of the treatment-group assignments, adjudicated safety and cardiovascular morbidity and mortality.

All 7-day Holters were analysed for the presence of sinus rhythm (primary endpoint) at a central core lab blinded for therapy. A data and safety monitoring board monitored safety of the patients and study progress.

Statistical analysis

The trial was designed to determine whether targeted therapy of underlying conditions is of added value to conventional therapy for sinus rhythm maintenance in patients with early persistent AF and HF. The primary analysis for efficacy consisted of a comparison of the occurrence of the primary endpoint between the targeted and the conventional rhythm control group by calculating the odds ratio (OR), with corresponding confidence limits according to the Miettinen–Nurminen method.[20] The null-hypothesis of no treatment benefit was rejected if the lower limit of the 95% confidence interval (95% CI) exceeded one, which is equivalent to two-sided testing at an alpha level of 0.05.[21] Corresponding *P*-values were calculated. The primary analysis was performed according to the intention-to-treat principle in the population of all randomised patients,

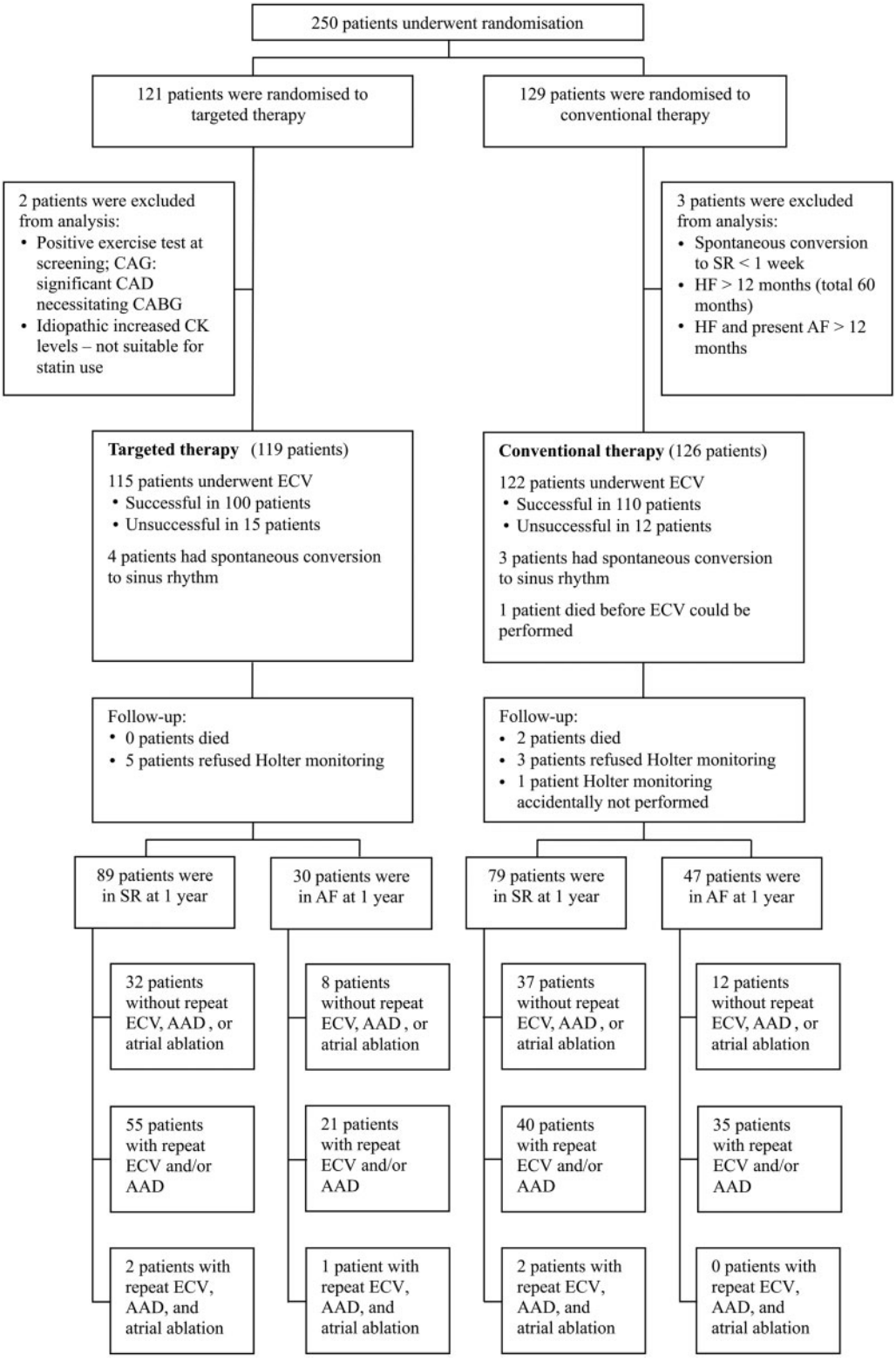


Figure 1 Trial profile. AAD, antiarrhythmic drugs; AF, atrial fibrillation; CAD, coronary artery disease; CAG, coronary angiogram; CABG, coronary artery bypass grafting; ECV, electrical cardioversion; ET, exercise test; HF, heart failure; SR, sinus rhythm.

Table 1 Baseline characteristics

Characteristics	Targeted therapy (*n* = 119)	Conventional therapy (*n* = 126)
Age (years)	64 ± 9	65 ± 9
Male sex	94 (79%)	99 (79%)
Total duration AF (months)	3 (2–7)	2 (2–5)
Total persistent AF (months)	2 (1–4)	2 (1–4)
Duration heart failure (months)	2 (1–4)	2 (1–4)
Hospital admission for HF	14 (12%)	22 (17%)
LVEF <45%	35 (29%)	37 (29%)
Hypertension	66 (55%)	78 (62%)
Diabetes	10 (8%)	16 (13%)
Coronary artery disease	19 (16%)	14 (11%)
Ischemic thromboembolic complication	6 (5%)	4 (3%)
Chronic obstructive pulmonary disease	9 (8%)	11 (9%)
CHA_2DS_2-VASc score[a]	2 (1–3)	2 (1–3)
Symptoms		
Palpitations	46 (39%)	55 (44%)
Dyspnoea	91 (76%)	102 (81%)
Fatigue	74 (62%)	72 (57%)
EHRA class	2 (2–2)	2 (2–2)
Body mass index (kg/m^2)	29 (26–31)	28 (25–31)
Blood pressure (mmHg)		
Systolic	130 ± 15	128 ± 15
Diastolic	83 ± 10	82 ± 10
Heart rate at rest in AF (beats/min)	87 (76–95)	88 (78–100)
NYHA classification		
I	28 (24%)	24 (19%)
II	80 (67%)	85 (68%)
III	11 (9%)	17 (13%)
NT-proBNP (pg/mL)	1057 (694–1636)	1039 (717–1755)
Medications		
Beta-Blocker	102 (86%)	108 (86%)
Verapamil/diltiazem	3 (3%)	11 (9%)
Digoxin	32 (27%)	32 (25%)
ACE-inhibitor	38 (32%)	48 (38%)
Angiotensin receptor blocker	24 (20%)	28 (22%)
Mineralocorticoid receptor antagonist	1 (1%)	3 (2%)
Statin[b]	40 (34%)	42 (33%)
Diuretic	51 (43%)	48 (38%)
Anticoagulant	116 (97%)	124 (98%)
Echocardiographic variables		
Left atrial size, long axis (mm)	43 (40–48)	44 (39–47)
Left atrial volume (mL/m^2)	38 (31–48)	38 (32–47)
LV ejection fraction (%)	50 (43–58)	50 (43–60)
Exercise test		
Maximum load (W)	134 (105–163)	125 (100–160)
24 h urine excretion		
Sodium (mmol/24 h)	160 (120–201)	162 (120–208)

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; LV, left ventricular; NT-proBNP, N-terminal pro-brain natriuretic peptide; W, Watts.
[a]The CHA_2DS_2-VASc score assesses thrombo-embolic risk. C, congestive heart failure/LV dysfunction; H, hypertension; A_2, age ≥75 years; D, diabetes mellitus; S_2, stroke/transient ischaemic attack/systemic embolism; V, vascular disease; A, age 65–74 years; Sc, sex category (female sex).

with the exception of those that unequivocally did not fulfil the inclusion criteria. As sensitivity analysis, we evaluated the primary endpoint in the population of patients in whom the 1-year Holter was available.

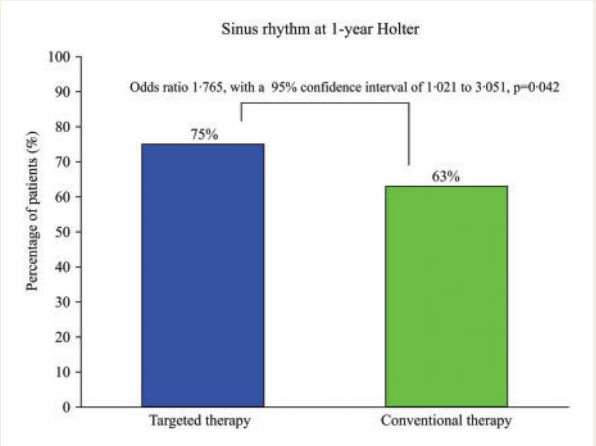
The study size was determined on the basis of an expected rate of the primary endpoint of 70% for the intervention group, and 50% for the conventional group. The total sample size of 100 patients in each group yielded 80% power for testing with a two-sided alpha of 0.05. After anticipating a dropout rate of 20%, total sample size was set at 250.

Subgroup analyses were conducted to evaluate treatment interactions within pre-specified subgroups. In the pre-specified subgroup analyses ORs and 95% CIs were calculated by the Miettinen–Nurminen method. *P*-values for interaction were obtained by logistic regression. The hazard ratio (HR) for the composite secondary endpoint was calculated using Cox regression analyses. We used the χ^2 or Fisher's exact test for categorical data or Student's *t*-test or Wilcoxon's two-sample test. Analyses were conducted with R [version 3.3.3 (www.r-project.org)] and SPSS (version 23 or higher) statistical packages. A two-sided *P*-value of <0.05 was considered statistically significant.

Results

Figure 1 shows the trial profile. We randomly assigned 250 patients to targeted therapy of underlying conditions or conventional therapy. Five patients were excluded because they did not fulfil the inclusion criteria. Of 245 patients, 119 were randomly assigned to targeted therapy and 126 to conventional therapy. Baseline characteristics were comparable (*Table 1*). BMI > 30 kg/m^2 was present in 90 (37%) patients, 29% of patients had HFrEF.

Table 2 lists the implementation of targeted therapy of underlying conditions at 1 year. *Figure 1* shows therapies and outcome during follow-up. The study intervention led to a contrast in MRA use (*n* = 101 [85%] vs. *n* = 5, [4%]; *P* < 0.001) and statin use (*n* = 111 [93%] vs. *n* = 61 [48%]; *P* < 0.001). At least three interventions were maintained in 87%, all therapies in 58% of patients. The numbers of patients with repeat ECV (67 [56%] vs. 64 [51%]; *P* = 0.443), total number of ECVs during the first 6 months (75 vs. 75; *P* = 0.807), and last 6 months (27 vs. 18, *P* = 0.138), institution of any antiarrhythmic drug (54 [45%] vs. 54 [43%]; *P* = 0.701), sotalol (21 [18%] vs. 16 [13%];



Take home figure Primary outcome established by 7-day Holter monitoring and clinical status.

$P = 0.291$), flecainide (13 [11%] vs. 9 [7%]; $P = 0.373$), dronedarone (1 [1%] vs. 2 [2%]; $P = 1.000$), amiodarone (26 [22%] vs. 31 [25%]; $P = 0.652$), and atrial ablations (3 [3%] vs. 2 [2%]; $P = 0.716$) were comparable (*Figure 1*).

At 1 year of follow-up, sinus rhythm was present in 89 of 119 patients (75%) in the intervention vs. 79 of 126 patients (63%) in the conventional group (OR 1.765, with a lower limit of the 95% CI of 1.021, 2-sided $P = 0.042$) (*Take home figure*). When the primary outcome analysis was restricted to patients with a 1-year Holter, sinus rhythm was present in 84 of 114 patients (74%) in the intervention vs. 76 of 120 patients (63%) in the conventional group (OR 1.621, with a lower limit of the 95% CI of 0.929, $P = 0.089$). Continuous sinus rhythm was present in 71 (62%) in the intervention vs. 63 patients (52%) in the conventional group (OR 1.494, with a lower limit of the 95% CI of 0.887, $P = 0.131$). The others had short episodes of self-terminating AF lasting less than one-seventh of the time at 7-day Holter (*Figure 2*). Median AF burden in these patients was 5.69% [interquartile range (IQR) 1.06–7.56%] in the

Table 2 Implementation of targeted therapy of underlying conditions at 1-year

	Targeted	Conventional	*P*-value
Intervention			
MRA	101 (85%)	5 (4%)	<0.001
Spironolactone (mg)	25 (25–50)	25 (20–25)	0.066
Eplerenon (mg)	50 (25–50)	25 (25–25)	0.101
Statins[a]	111 (93%)	61 (48%)	<0.001
Simvastatin (mg)	40 (25–40)	40 (25–40)	0.789
Rosuvastatin (mg)	10 (6–10)	10 (10–20)	0.050
ACE-inhibitor and/or ARB[a]	103 (87%)	96 (76%)	0.094
Enalapril (mg)	20 (5–20)	20 (12–20)	0.748
Perindopril (mg)	4 (2–8)	4 (4–8)	0.306
Losartan (mg)	50 (50–100)	100 (50–100)	0.283
Telmisartan (mg)	40 (20–80)	40 (40–80)	0.419
Cardiac rehabilitation and physical activity during follow-up[b]	109 (92%)	–	–
Supervised cardiac rehabilitation	110 (92%)	–	–
Physical activity during follow-up	109 (92%)	–	–
Duration >150 min/week	82 (69%)	–	–

Data are number of patients (%) or median (IQR).
ARB, angiotensin-receptor blocker; ACE, angiotensin-converting enzyme; MRA, mineralocorticoid receptor antagonist; -, not available.
[a]Only dosages of most commonly used drugs provided.
[b]Includes both cardiac rehabilitation supervised training and continued activity during 1 year of follow-up ≥3/week.

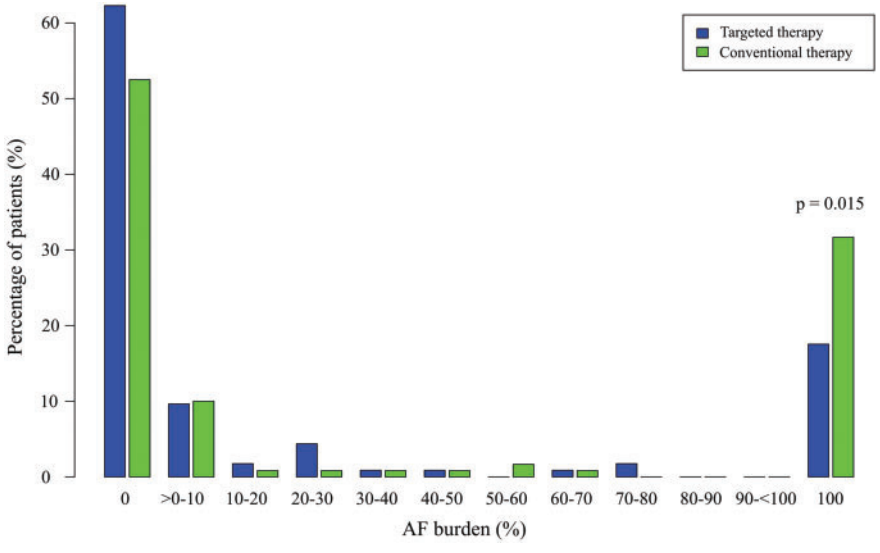


Figure 2 Distribution of atrial fibrillation burden during 7-day Holter.

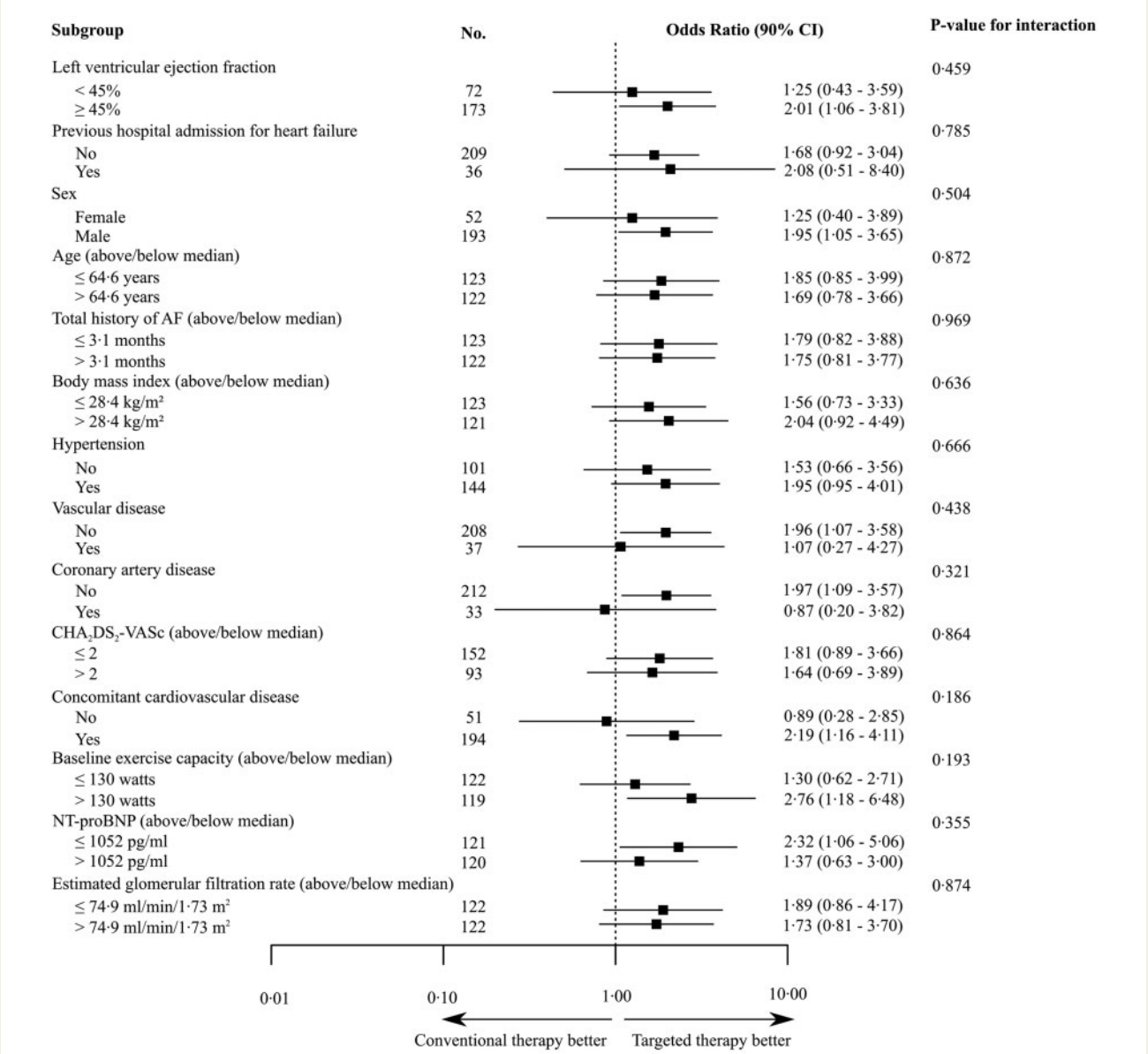


Figure 3 Forest plot showing no significant treatment interactions. The CHA_2DS_2-VASc score is a measure of thrombo-embolic risk.

intervention vs. 1.38% (IQR 0.29–3.12%), $P = 0.144$, in the conventional group.

The effects of targeted therapy of underlying conditions in 14 prespecified subgroups were consistent among subgroups without statistically significant interactions (*Figure 3*).

At 1 year of follow-up, modification (represented as delta) of blood pressures, NT-proBNP, weight, BMI, and lipid profile was significantly more successfully accomplished in the targeted therapy group (*Table 3*). Left ventricular ejection fraction improved in both groups, most outspoken in HFrEF patients, and symptoms decreased, even more in the intervention group (*Table 3*). Atrial fibrillation associated hospital admissions accounted for about half of cardiovascular hospital admissions without significant differences between the groups (hazard ratio 0.83 [95% CI 0.33-2.10, $P = 0.690$] for the composite endpoint, *Table 4*). Any adverse event was observed in 48 (40%) patients vs. 9 (7%) patients in the intervention vs. conventional group, necessitating drug discontinuation in 12 (10%) vs. 1 (1%) patients, respectively. The most frequently encountered drug-associated adverse events associated with MRA use were increased potassium levels and renal function impairment necessitating discontinuation in seven patients (6%) (*Table 5*).

Discussion

We found that in patients with short lasting AF and HF targeted therapy of underlying conditions was of value for reduction of blood pressure and lipid levels, and improvement of HF. In addition, on top of the beneficial effects on underlying conditions, this strategy improved

Table 3 Change in secondary endpoints at 1-year follow-up

Characteristic	Targeted ($n = 119$)	Conventional ($n = 126$)	Δ targeted (baseline vs. 1-year)%	Δ conventional baseline vs. 1-year)%	*P*-value Δ targeted vs. conventional
Risk factors					
Systolic blood pressure (mmHg)					
Baseline	130.5 ± 15.5	128.2 ± 14.5			
1-year	125.2 ± 15.3	129.6 ± 16.1	-3.28%	2.05%	0.004
Diastolic blood pressure (mmHg)					
Baseline	83.4 ± 10.5	81.6 ± 9.9			
1-year	75.2 ± 9.7	78.8 ± 9.9	-8.95%	-2.31%	<0.001
Body mass index (kg/m^2)					
Baseline	28.7 (25.9–31.1)	28.1 (25.4–31.1)			
1-year	28.5 (26.0–31.2)	28.1 (26.1–31.5)	0.12%	1.37%	0.023
Weight (kg)					
Baseline	93.3 ± 13.8	90.0 ± 14.5			
1-year	93.3 ± 14.5	91.3 ± 15.1	-0.13%	1.35%	0.025
NT-proBNP (pg/mL)					
Baseline	1057 (694–1636)	1039 (717–1755)			
1-year	178 (90–381)	258 (130–924)	-67.25%	-37.26%	0.014
Total cholesterol (mmol/L)					
Baseline	5.0 ± 1.2	5.0 ± 1.2			
1-year	4.2 ± 0.9	4.9 ± 1.1	-13.21%	1.65%	<0.001
LDL Cholesterol (mmol/L)					
Baseline	3.0 ± 1.1	3.1 ± 1.0			
1-year	2.2 ± 0.7	3.0 ± 1.0	-18.37%	0.40%	<0.001
Urine sodium (mmol/24 h)					
Baseline	160 (120–201)	162 (120–208)			
1-year	156 (125–193)	179 (133–222)	5.39%	16.67%	0.354
AF symptoms					
EHRA class					
Baseline	2.0 (2.0–2.0)	2.0 (2.0–2.0)			
1-year	1.0 (1.0–2.0)	1.0 (1.0–2.0)	-31.01%	-23.71%	0.065
Palpitations, *n* (%)					
Baseline	46 (39%)	55 (44%)			
1-year	14 (12%)	19 (15%)	-68.51%	-64.61%	0.704
Dyspnoea, *n* (%)					
Baseline	91 (76%)	102 (81%)			
1-year	27 (23%)	30 (24%)	-69.30%	-69.87%	0.928
Fatigue, *n* (%)					
Baseline	74 (62%)	72 (57%)			
1-year	30 (26%)	31 (25%)	-58.05%	-55.89%	0.817
Secondary endpoints					
Left atrial volume (mL)					
Baseline	82 (65–99)	79 (65–95)			
Month 12	74 (64–87)	74 (58–94)	0.79%	2.40%	0.634
LVEF (%)					
Total population					
Baseline	50 (43–58)	50 (43–60)			
1-year	58 (55–60)	56 (52–60)	18.59%	15.67%	0.418
LVEF <45%					
Baseline	38 (33–40)	39 (32–40)			
1-year	56 (52–60)	55 (48–58)	48.35%	43.60%	0.528
LVEF ≥45%					
Baseline	55 (50–60)	55 (50–60)			
1-year	60 (55–60)	57 (54–60)	6.62%	4.37%	0.253

Continued

Table 3 *Continued*

Characteristic	Targeted ($n = 119$)	Conventional ($n = 126$)	Δ targeted (baseline vs. 1-year)%	Δ conventional baseline vs. 1-year)%	*P*-value Δ targeted vs. conventional
Safety endpoints					
Potassium (mmol/L)					
Baseline	4.3±0.4	4.3±0.4			
1-year	4.3±0.3	4.2±0.4	1.05%	-1.64%	0.030

Data are mean (SD), number of patients (%), or median (IQR). Delta represents mean change at 1-year follow-up in percentages.
ALT, alanine aminotransferase; EGFR, estimated glomerular filtration fraction; EHRA, European Heart Rhythm Association class for symptoms; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 4 Cardiovascular morbidity and mortality

Outcome	Intervention ($n = 119$)	Conventional ($n = 126$)
Composite secondary endpoint	18 (16%)	22 (17%)
Components		
All-cause mortality	0 (0%)	2 (2%)
Hospital admission for heart failure	0 (0%)	2 (2%)
Hospital admissions for atrial fibrillation	8 (7%)	10 (8%)
Hospital admissions for other cardiovascular reasons	10 (8%)	8 (6%)

Data are number of patients (%).

Table 5 Safety endpoints

Variable	Targeted ($n = 119$)	Conventional ($n = 126$)
MRA		
Medication associated AE	37 (31%)	0 (0%)
Increased potassium	13 (11%)	
Decreased renal function	14 (12%)	
Gynaecomastia	7 (6%)	
Other	3 (3%)	
Intervention		
Dose reduction	20 (17%)	
Replaced	3 (3%)	
Discontinuation	7 (6%)	
None	7 (6%)	
Physical activity		
Associated AE	1 (1%)	0 (0%)
NSTEMI	1 (1%)	
Intervention		
Discontinuation	1 (1%)	
Statin		
Medication associated AE	20 (17%)	4 (3%)
Myalgia	18 (15%)	4 (3%)
Elevated liver enzymes	2 (2%)	0 (0%)
Intervention		
Dose reduction	4 (3%)	1 (1%)
Replaced	8 (7%)	2 (2%)
Discontinuation	3 (3%)	1 (1%)
None	5 (4%)	0 (0%)
ACE-I and/or ARB		
Medication associated AE	13 (10%)	7 (6%)
Tickling cough	5 (4%)	3 (2%)
Dizziness	6 (5%)	0 (0%)
Decreased renal function	2 (2%)	4 (3%)
Intervention		
Dose reduction	7 (6%)	4 (3%)
Replaced	5 (4%)	3 (2%)
Discontinuation	1 (1%)	0 (0%)

Data are number of patients (%).
AE, adverse event; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; MRA, mineralocorticoid receptor antagonist; NSTEMI, non-ST segment elevation myocardial infarction.

maintenance of sinus rhythm. The primary outcome was present in 75% of patients in the intervention vs. 63% in the conventional group, which translates in a relative risk reduction of 32%. The present study therefore confirms and further extends prior studies.

Previous studies on upstream therapy addressing the underlying substrate and instituted for secondary prevention of AF have been disappointing.[10,22] Recently, however, evidence has become available that interventions aiming to reduce major underlying conditions of AF are able to decrease incident AF and AF burden, on top of improving underlying conditions. Beneficial effects were observed in obese patients undergoing lifestyle changes including weight reduction and improvement of fitness,[13,14] hypertensive patients receiving antihypertensive therapy,[18,23,24] and HF patients instituted on optimal HF therapy.[12]

Yet, not all studies addressing hypertension were successful.[25] Least evidence is available for statins, although being assessed predominantly in post-operative AF.[26]

The present study, however, was different from prior studies for two reasons. First, in order to improve outcome, this study contained four therapies. MRAs were dosed as high as possible, contributing in combination with ACE-Is and ARBs, to blood pressure control and HF therapy.[27] Of note, HFpEF is frequently disregarded in AF patients since it is often difficult to diagnose because symptoms and signs of AF and HFpEF are often similar.[28] Statins were instituted for optimal therapy of vascular disease.[9] A greater reduction in blood

pressure, NT-proBNP and cholesterol levels was indeed achieved in the intervention group. In addition, MRAs, ACE-I, and ARBs may have contributed to maintenance of sinus rhythm due to their anti-fibrotic effects,[11,12] and statins due to their anti-inflammatory effects.[4,10,26] Although its effect on weight and BMI reduction was modest, cardiac rehabilitation may have had an additional positive effect on underlying conditions including blood pressure and lipid profile.[16] In addition, being also an educational intervention, this program may have contributed to adherence to therapies and fits into the emerging concept of integrated AF care and shared decision-making.[6,16] Which one of the four interventions was most effective cannot be concluded from the present data. However, it was our intention to target a combination of underlying cardiovascular conditions, in combination with an educational intervention. Adverse events were not trivial. However, only a minority of patients discontinued their intervention therapies.

Secondly, we aimed to include persistent AF patients earlier after start of the underlying condition and of AF, thus earlier during the remodelling process.[5,8,29] Although a total AF history of 5 years is not short, the duration of persistent AF had to be less than 6 months, shorter than in many prior trials. However, in hindsight, our patients were not so 'early' in the remodelling process as intended, which was also reflected by the number of ECVs during follow-up. No change in atrial size during follow-up was observed which may also be due to the latter. On the other hand, it might well be that atrial size does not really reflect atrial remodelling. Of interest, a small percentage of patients showed regression from persistent to paroxysmal self-terminating AF which reflects reversion to a more beneficial type of AF.

Limitations of the present study comprise the small number of patients, enrolment of a rather selective cohort of persistent AF patients, the open design, and the absence of data on physical activity in the conventional group. Additionally, the inclusion rate was slower than expected, but constant over the years. Although it would be of interest to assess which strategy had a significant impact on outcome, the design of our study precluded such analysis. Cardiac rehabilitation including physical activity was elaborate and may be difficult to implement. Finally, a follow-up period of 1 year is too short to prove benefit of targeted therapy. Therefore, it is relevant to assess whether long-term therapy is associated with a more pronounced difference in sinus rhythm maintenance. This is currently investigated in our long-term follow-up. Strengths of the study include a randomized trial, multicentre design, comparable institution of rhythm control therapy in both study groups, and pre-specified outcomes.

The present results are relevant since a strategy focusing on targeting of underlying conditions in patients with AF and HF showed a favourable effect on underlying conditions in association with a modest effect on sinus rhythm maintenance. Although the number of repeated ECVs and institution of antiarrhythmic drugs was not small, our study may contribute to a better understanding of success of rhythm control therapy.

In conclusion, targeted therapy of underlying conditions in patients with AF and HF was effective to improve blood pressure, lipid profile, weight, BMI, and HF. In addition, on top of that, it was of added value to improve maintenance of sinus rhythm. Therefore, our study may contribute to the shift to focus on early management of underlying conditions to improve AF outcomes.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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