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LETTER TO THE EDITORS

Determinants of sinus rhythm maintenance in patients with early-persistent atrial fibrillation and heart failure

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Sirs:

Atrial fibrillation (AF) and heart failure (HF) often coexist. Rate versus rhythm control trials showed no differences in outcome, which can in part be accounted for the inability to maintain sinus rhythm, and lack of direct interference of antiarrhythmic drugs with cardiovascular risk factors underlying AF progression [1]. It has been shown that the more advanced types of AF have worse outcome, suggesting that sinus rhythm maintenance may be of importance [2]. Recently, the Routine versus Aggressive risk factor-driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) trial showed that the targeted therapy of underlying conditions was superior in sinus rhythm maintenance during 1-year follow-up in patients with early-persistent AF and HF [3]. In the current manuscript, we aimed to identify factors associated with sinus rhythm maintenance in patients with a short history of persistent AF and HF included in the RACE 3.

The RACE 3 design was described previously [3]. In short, patients with early symptomatic persistent AF and early HF were included. Total AF history up to 5 years was allowed (total persistent AF duration > 7 days but < 6 months, ≤ 1 electrical cardioversion). Patients with both HF with a preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) were eligible. 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. 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. Patients were randomized to targeted therapy of underlying conditions or conventional therapy and subsequently received a cardioversion. On top of conventional therapy, targeted therapy received four additional therapies: mineralocorticoid receptor antagonists, statins, angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, and cardiac rehabilitation including physical therapy, dietary restrictions and counseling. Primary outcome was sinus rhythm maintenance at 1-year follow-up, assessed by 7-day Holter. Sinus rhythm maintenance was defined as sinus rhythm ≥ 6/7th of the time during the 7-day Holter. The study was approved by the institutional review board and was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent.

The association of sinus rhythm maintenance with baseline clinical and echocardiographic parameters was tested by univariable logistic regression. All factors with a univariable P value < 0.1 were used to create a stepwise multivariable logistic regression model for sinus rhythm maintenance. The final model was tested for significant interactions and collinearity. Odds ratios (OR) and 95% confidence intervals (CI) were given. The model was adjusted for randomization strategy, as targeted therapy showed to be superior in sinus rhythm maintenance [3]. As sensitivity analysis, 100% sinus rhythm at the 7-day Holter was additionally used as outcome parameter, instead of ≥ 6/7th of the time. A P value < 0.05 was considered statistically significant. Thromboembolic complications were defined as stroke, transient ischemic attack of pulmonary embolism.

All 245 RACE 3 patients were included in the present analysis. Table 1 shows the baseline characteristics of the trial population.

Sinus rhythm maintenance at 1 year was observed in 168 (69%). A total of three variables had a univariable

Trial Registration number: Clinicaltrials.gov NCT00877643.

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Table 1 Baseline characteristics for the study population and split based on the rhythm on the 7-day Holter at 1 year

Characteristics	Total ($n=245$)	SR at 1 year ($n=168$)	AF at 1 year ($n=77$)	P value (between groups)
Age (years)	65 ± 9	65 ± 9	65 ± 9	0.527
Male sex	193 (79%)	134 (80%)	59 (77%)	0.615
Hypertension	144 (59%)	98 (58%)	46 (60%)	0.889
Diabetes	26 (11%)	12 (7%)	14 (18%)	0.009
Coronary artery disease	33 (14%)	23 (14%)	10 (13%)	0.881
Ischemic thromboembolic complication	10 (4%)	4 (2%)	6 (8%)	0.076
Chronic obstructive pulmonary disease	20 (8%)	12 (7%)	8 (10%)	0.452
CHA_2DS_2-VASc score*	2 (1–3)	2 (1–3)	2 (1–3)	0.302
Body mass index (kg/m^2)	28 (26–31)	29 (26–32)	28 (26–31)	0.628
Blood pressure (mmHg)				
Systolic	129 ± 15	129 ± 15	130 ± 16	0.669
Diastolic	83 ± 10	83 ± 10	82 ± 10	0.800
Left atrial size, long axis (mm)	43 (40–47)	44 (39–47)	43 (40–47)	0.811
Left atrial volume (mL)	80 (65–97)	82 (66–100)	73 (56–95)	0.051
LVEF (%)	50 (43–59)	50 (50–58)	54 (45–60)	0.363

Data are mean (standard deviation), number of patients (%), or median (interquartile range)

C congestive heart failure/LV dysfunction, *H* hypertension, A_2 age ≥ 75 years, *D* diabetes mellitus; S_2 stroke/transient ischemic attack/systemic embolism, *V* vascular disease, *A* age 65–74 years, *Sc* sex category (female sex)

*The CHA_2DS_2-VASc score assesses thromboembolic risk

P value < 0.1, including prior ischemic thromboembolic events (OR 0.289, 95% CI 0.079–1.054, $P=0.060$), diabetes (OR 0.346, 95% CI 0.152–0.790, $P=0.012$) and left atrial volume (OR 1.014, 95% CI 1.001–1.027, $P=0.033$). In multivariable logistic regression analysis, prior ischemic thromboembolic complications and diabetes were both negatively associated with sinus rhythm maintenance (Fig. 1). In a sensitivity analysis, both thromboembolic complications (OR 0.160, 95% CI 0.033–0.782, $P=0.024$) and diabetes (OR 0.412, 95% CI 0.170–0.995, $P=0.049$) remained negatively associated with 100% sinus rhythm maintenance. No factors were associated with sinus rhythm maintenance in both randomization groups separately.

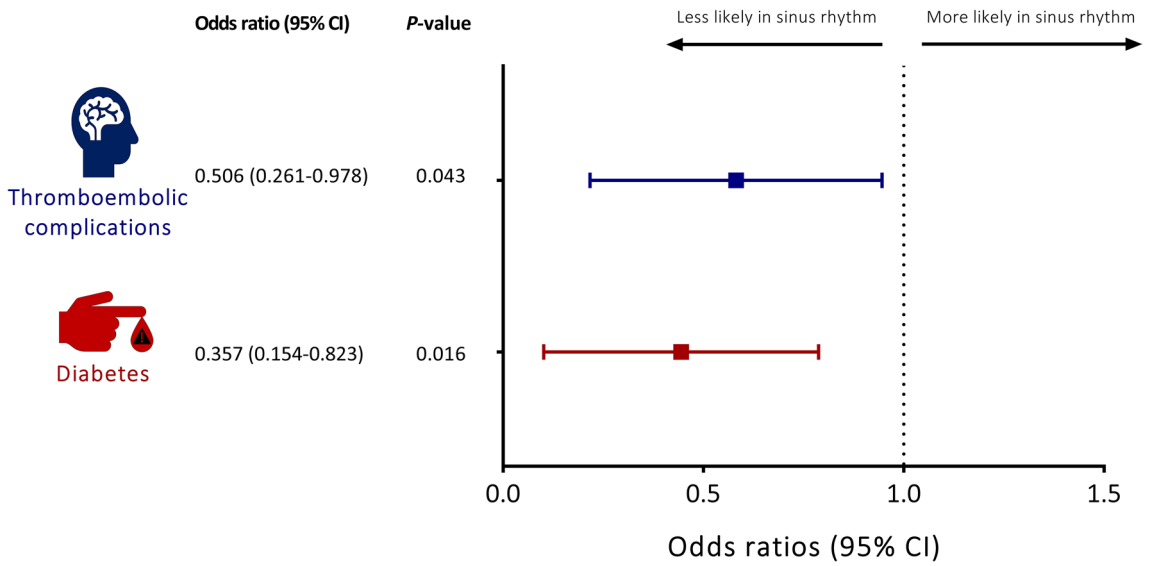

Fig. 1 Multivariable associated with sinus rhythm maintenance, adjusted for randomization strategy. *CI* confidence interval

Baseline levels of HbA1c were similar in patients who were in sinus rhythm at 1 year and who were in AF [40 (37–43) versus 41 (38–46), $P=0.126$]. But at 1 year, HbA1c was significantly lower in patients who were in sinus rhythm, compared to patients who were in AF [38.5 (36–42) versus 42 (37.5–46), $P=0.002$].

We showed that in patients with early-persistent AF and HF, both prior thromboembolic complications and diabetes were negatively associated with sinus rhythm maintenance.

Preventing thromboembolic complications, including stroke, is one of the pillars for AF treatment [4]. Risk of stroke is generally increased by the number of underlying risk factors and age, indicating that patients with more underlying (heart) disease and advanced age are at higher risk of stroke. More underlying conditions result in more advanced cardiac remodeling, explaining the inverse relation to sinus rhythm maintenance in patients with prior thromboembolic complications. Also, asymptomatic AF may be detected years after onset, allowing atrial remodeling to continue. This can result in stroke being the first symptom of underlying AF. Secondly, stroke can be a result of undiagnosed vascular disease (e.g. carotid artery plaques). As previously mentioned, Weijs et al. showed that vascular disease is often present, even in patients originally diagnosed as having 'lone AF' [5]. Lastly, thromboembolic complications can be a result of a hypercoagulable state that is often found in AF [6]. A hypercoagulable state can result both in stroke and atrial fibrosis through protease-activated receptor stimulation [7].

Diabetes is a notorious risk factor for AF and affects multiple organs, as well as endothelial function. This can in turn enhance vascular and atrial remodeling, which promotes progression of AF and thus the inability to maintain sinus rhythm. An analysis from Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) found diabetes to be associated with higher risk of mortality in AF [8]. Question remains whether diabetes increases AF risk independent of other risk factors. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) showed no differences in AF incidence in patients with intensified glucose control, compared to conventional control [9]. This implicates that diabetes-related complications are hard to prevent by adequate treatment. We showed that Hb1Ac was lower in patients receiving targeted therapy of underlying conditions at 1 year follow-up. Whether this indicates that targeted therapy improves glucose tolerance—and could thereby lower the risk on diabetes—is not to be concluded from these data and clearly warrants further research [10].

Limitations of the current manuscript include the moderate sample size, which limits the power to perform subgroup analyses. Additionally, all associations found do not necessarily reflect causal relations, which may also be considered a limitation.

In conclusion, both diabetes and a history of thromboembolic complications were negatively associated with sinus rhythm maintenance in patients with early-persistent AF and HF.

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