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The impact of supraventricular ectopic complexes in different age groups and risk of recurrent atrial fibrillation after antiarrhythmic medication or catheter ablation

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ABSTRACT

Introduction: Supraventricular ectopic complexes (SVEC) are known risk factors of recurrent atrial fibrillation (AF). However, the impact of SVEC in different age groups is unknown. We aimed to investigate the risk of AF recurrence with higher SVEC burden in patients ±57 years, respectively, after treatment with antiarrhythmic medication (AAD) or catheter ablation (CA).
Methods: In total, 260 patients with LVEF >40% and age ≤70 years were randomized to AAD (N = 132) or CA (N = 128) as first-line treatment for paroxysmal AF. All patients underwent 7-day Holter monitoring at baseline, and after 3, 6, 12, 18 and 24 months and were categorized according to median age ±57 years. We used multivariate Cox regression analyses and we defined high SVEC burden at 3 months of follow-up as the upper 75th percentile >195 SVEC/day. AF recurrence was defined as AF ≥1 min, AF-related cardioversion or hospitalization.
Results: Age >57 years were significantly associated with higher AF recurrence rate after CA (58% vs 36%, p = 0.02). After CA, we observed a higher SVEC burden during follow-up in patients >57 years which was not observed in the younger age group treated with CA (p = 0.006). High SVEC burden at 3 months after CA was associated with AF recurrence in older patients but not in younger patients (>57 years: HR 3.4 [1.4–7.9], p = 0.005). We did not find any age-related differences after AAD.
Conclusion: We found that younger and older patients respond differently to CA and that SVEC burden was only associated with AF recurrence in older patients.

1. Introduction

The initiation and maintenance of atrial fibrillation (AF) requires a trigger that initiates the arrhythmia and the presence of a predisposing substrate that perpetuates it [1]. Supraventricular ectopic complexes (SVEC) originating in the pulmonary veins are known triggers of paroxysmal AF [2,3] and atrial enlargement, atrial fibrosis and loss of myocardial tissue among others are considered substrate for perpetuation of AF [1,4].

The incidence of AF increases dramatically with increasing age [5,6] which may be attributed to atrial remodeling characterized by anatomical and structural changes, reduction in atrial voltage, widespread conduction slowing as well as sinus node dysfunction associated with aging [7–9]. These changes may represent age-related development of atrial fibrosis which may be responsible for the increased susceptibility to AF with increasing age [8].

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However, the importance of supraventricular ectopic triggers in the initiation of recurrent AF between different age groups has not previously been investigated. Hence, our aim was two-fold; first, we aimed to investigate the prevalence of SVEC in younger patients as compared to older patients after treatment with antiarrhythmic medication and catheter ablation, respectively. Secondly, we aimed to investigate the risk of AF recurrence according to SVEC burden at 3 months of follow-up in patients <57 years and patients aged 57–70 years, respectively, after antiarrhythmic medication and catheter ablation, respectively.

2. Methods

2.1. Patient selection

The *Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation* (MANTRA-PAF) trial included 294 patients with symptomatic paroxysmal AF naive to antiarrhythmic medication. Patients were 18–70 years of age with no structural or valvular heart disease. Patients with left ventricular ejection fraction (LVEF) <40% or left atrial diameter >50 mm were excluded. Information about the study protocol and primary results have been published previously [10,11].

Patients were randomly assigned to treatment with either antiarrhythmic medication or catheter ablation. We excluded two patients randomized to antiarrhythmic medication who did not receive the index treatment and 6 patients randomized to catheter ablation who did not undergo the ablation procedure. Furthermore, 26 patients who did not have a readable Holter monitoring at baseline were excluded. The remaining 260 patients were included in the current study, 132 randomized to and treated with antiarrhythmic medication and 128 patients randomized and treated with catheter ablation.

First-line antiarrhythmic medication was flecainide at a dose of 200 mg per day or propafenone at a dose of 600 mg per day. In patients with contraindications for class IC antiarrhythmic drugs amiodarone at a dose of 200 mg per day or sotalol at a dose of 160 mg per day were used. In total, 123 (93%) were treated with flecainide, 4 (3%) with amiodarone, 2 (2%) with propafenone and 3 (2%) had sotalol as initial treatment. A β-blocker, calcium-channel blocker or digoxin was given supplementary to class IC agents according to institutional standards at the involved centers. A detailed overview of the medication has previously been reported [11].

Wide antral ablation with encircling of ipsilateral veins combined with a supplementary linear ablation line placed along the roof of the left atrium between the two encircled areas using either a 3.5-mm catheter with an irrigated tip or 8 mm solid-tip catheter were mandatory. Other ablation lines were optional. The endpoint was absence of high-frequency electrical activity (>0.2 mV) inside the encircled areas around the pulmonary veins documented by electroanatomic mapping (CARTO, Biosense Webster). Patients randomized to catheter ablation with AF recurrence were offered additional procedures where the left atrium and pulmonary veins were explored and re-conduction was identified guided by CARTO-mapping and re-isolation of the pulmonary veins was performed at the operator's discretion.

Patients randomized and treated with antiarrhythmic medication who during follow-up underwent supplementary catheter ablation and patients randomized and treated with catheter ablation who had supplementary antiarrhythmic medication during follow-up were censored at the time of crossover.

All patients underwent 7-day continuous Holter monitoring prior to treatment start, and after 3, 6, 12, 18, and 24 months of follow-up. Furthermore, patients were also instructed to contact the study center if they had palpitations or other symptoms between the follow-up visits.

2.2. Definitions

The recordings were both automatically and visually controlled by an independent blinded technician using Sentinel Pathfinder Digital (Spacelabs Healthcare) and all automatically detected SVECs were reevaluated by the responsible cardiologist. A SVEC was defined by a coupling interval to the preceding QRS complex 70% of the mean RR of basic rhythm before the event and an interval QRS duration of 0.12 s unless aberration was suspected. Finally, the post-contraction pause had to be non-compensatory. To account for variations in recording time, SVEC burden was reported as median number supraventricular ectopic complexes per day occurring in sinus rhythm. Baseline AF burden was defined as the percentage of time on Holter recordings at baseline. For both treatment groups, a composite of any recurrence of ECG or Holter documented sustained AF ≥1 min duration, cardioversion for AF or hospitalization due to AF after a 3-month blanking period and during the 24-month follow-up was defined as the endpoint.

To derive a clinically meaningful cut-off for the severely right-skewed distribution of SVEC, we set the cut-off value at the top 75th percentile for the frequency of SVEC. Thus, we defined high SVEC burden as >195 SVEC/day at 3 months' follow-up. In order to investigate the prevalence of SVEC with increasing age patients were categorized according to median age; age <57 years and 57–70 years, respectively.

2.3. Ethics

All patients provided written informed consent before inclusion. The regional ethics committees approved the study. The study was in compliance with the Helsinki Declaration. No gender based differences were present.

2.4. Statistical analysis

Comparisons of baseline characteristics according to age <57 and 57–70 years were made with Student's *t*-test for continuous variables and χ^2 test or Fisher's exact test for categorical variables. For normally distributed variables mean and standard deviation (SD) are presented; otherwise median value and interquartile range are presented. Non-normally distributed continuous variables are presented as median with interquartile range (IQR) and were compared with Wilcoxon rank sum test.

To compare the difference in median SVEC burden between patients aged <57 years and 57–70 years after antiarrhythmic medication and catheter ablation, respectively, Wilcoxon rank sum test was used.

Kaplan Meier plots with log-rank test were used to illustrate time to AF recurrence in patients <57 years and 57–70 years for each treatment group. In order to estimate the risk of AF recurrence in relation to age group and SVEC burden we used univariate and multivariate Cox proportional hazards regression models. Baseline variables associated with AF recurrence in the univariate analyses were included in the multivariate analysis.

To test the discriminatory performance of SVEC burden to predict AF recurrence sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated using receiver operating characteristic curves.

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, US). Two-tailed tests of significance were reported and p-values <0.05 were considered statistically significant.

3. Results

3.1. Study population

Patient characteristics are reported according to treatment group in Table 1. Due to the randomized design, there were no differences in patient characteristics. Table 2 illustrates patient characteristics according to age-group in each treatment group. In the antiarrhythmic medication group, more patients aged 57–70 years were women and more patients

Table 1
Patient characteristics stratified by treatment group.

	AAD	Catheter Ablation	P
	n = 132	n = 128	
Age (sd)	54 (10)	56(9)	0.2
Female sex	36 (27)	38 (30)	0.8
Blood pressure, mmHg (sd)			
Systolic	135 (17)	138 (20)	0.2
Diastolic	81 (10)	81 (9)	0.9
BMI, kg/m^2 (sd)	27 (4)	27 (4)	0.4
Hypertension (%)	45 (34)	36 (28)	0.4
CAD (%)	2 (2)	5 (4)	0.3
Valvular disease (%)	9 (7)	2 (2)	0.1
Previous valve intervention (%)	1 (1)	1 (1)	0.9
Pacemaker (%)	6 (5)	5 (4)	1.0
Diabetes (%)	7 (5)	5 (4)	0.8
Ischemic stroke or TIA (%)	4 (3)	0 (0.0)	0.1
COPD (%)	6 (5)	6 (5)	1.0
Thyroid disease (%)	7 (5)	8 (6)	0.8
Left atrial size, mm (sd)	40 (5)	40 (5)	0.2
LVEF, % (sd)	64 (8)	64 (10)	0.8
Beta-blocker (%)	94 (71)	91 (71)	1.0
Calcium blocker (%)	14 (11)	26 (20)	0.05
Digoxin (%)	10 (8)	12 (9)	0.8
SVEC burden, median (IQR)	79 (IQR 22–416)	82 (31–269)	0.8
AF burden[a], % (IQR)	1.1 (0–11.9)	2.3 (0–14.8)	0.5

[a] Percent of time in atrial fibrillation during 7-day Holter recording at baseline. Continuous variables are presented as mean (SD) and categorical variables as number (%). Non-normally distributed variables SVEC burden and AF burden are presented as median with interquartile range (IQR). SVEC indicates supraventricular ectopic complexes; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; SD standard deviation; yr years; AF atrial fibrillation.

Table 2
Patient characteristics by age group in each treatment group.

	AAD			Catheter ablation		
	<57 years	57–70 years	P	<57 years	57–70 years	P
	n = 64	n = 68		n = 70	n = 58	
Age (sd)	47 (8)	62 (4)	<0.001	48 (8)	62 (4)	<0.001
Female sex (%)	12 (18)	24 (38)	0.02	17 (29)	21 (30)	1.0
Blood pressure, mmHg (sd)						
Systolic (sd)	133 (15)	138 (19)	0.1	137 (20)	139 (20)	0.4
Diastolic (sd)	82 (10)	81 (11)	0.5	81 (9)	82 (9)	0.5
BMI, kg/m^2 (sd)	27 (4)	26 (4)	0.6	28 (4)	26 (4)	0.06
Hypertension (%)	17 (25)	28 (44)	0.04	13 (22)	23 (33)	0.3
CAD (%)	1 (2)	1 (2)	1.0	3 (5)	2 (3)	0.7
Valvular disease (%)	0 (0.0)	9 (14)	0.001	0 (0)	2 (3)	0.5
Valve intervention (%)	0 (0.0)	1 (1.6)	1.0	0 (0)	1 (1)	0.3
Pacemaker (%)	0 (0.0)	6 (9)	0.01	0 (0)	5 (7)	0.06
Diabetes (%)	6 (9)	1 (2)	0.1	3 (5)	2 (3)	0.8
Stroke or TIA (%)	0 (0.0)	4 (6)	0.05	0	0	NA
COPD (%)	2 (3)	4 (6)	0.6	3 (5)	3 (4)	1.0
Thyroid disease (%)	4 (6)	3 (5)	1.0	5 (9)	3 (4)	0.5
Left atrial size, mm (sd)	38 (5)	41 (5)	0.01	40 (5)	41 (6)	0.4
LVEF, % (sd)	66 (8)	63 (7)	0.02	64 (9)	64 (10)	0.8
Beta-blocker (%)	44 (65)	50 (78)	0.1	38 (66)	53 (76)	0.3
Calcium blocker (%)	3 (4)	11 (17)	0.04	9 (16)	17 (24)	0.3
Digoxin (%)	4 (6)	6 (9)	0.7	3 (5)	9 (13)	0.2
AF burden[a], % (IQR)	2.6 (0–9.7)	0.6 (0–13.2)	0.8	0.6 (0–15.7)	3.7 (0–14.8)	0.7

[a] Percent of time in atrial fibrillation during 7-day Holter recording at baseline. Continuous variables are presented as mean (SD) and categorical variables as number (%). Non-normally distributed variables SVEC burden and AF burden are presented as median with interquartile range (IQR). SVEC indicates supraventricular ectopic complexes; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; SD standard deviation; yr years; AF atrial fibrillation.

had hypertension, and slightly lower LVEF. In patients treated with catheter ablation we found no difference in comorbidities.

3.2. Age and risk of AF recurrence

Fig. 1 illustrates that patients <57 years undergoing catheter ablation had a significantly lower AF recurrence rate as compared to patients aged 57–70 years (Fig. 1B) and both age groups treated with AAD (Fig. 1A). Higher age was associated with a significantly higher AF recurrence after catheter ablation (HR 1.9 [1.1–3.2], p = 0.02) but not in patients treated with antiarrhythmic medication (HR 0.9 [0.6–1.6], p = 0.8, p = 0.02 for interaction, Fig. 1C).

3.3. SVEC burden and risk of AF recurrence

We further investigated SVEC burden according to age group at baseline and during 24-months follow-up in patients treated with antiarrhythmic medication (Fig. 2A) and catheter ablation (Fig. 2B). Patients aged 57–70 years had a significantly higher SVEC burden during follow-up after catheter ablation as compared to patients <57 years. In

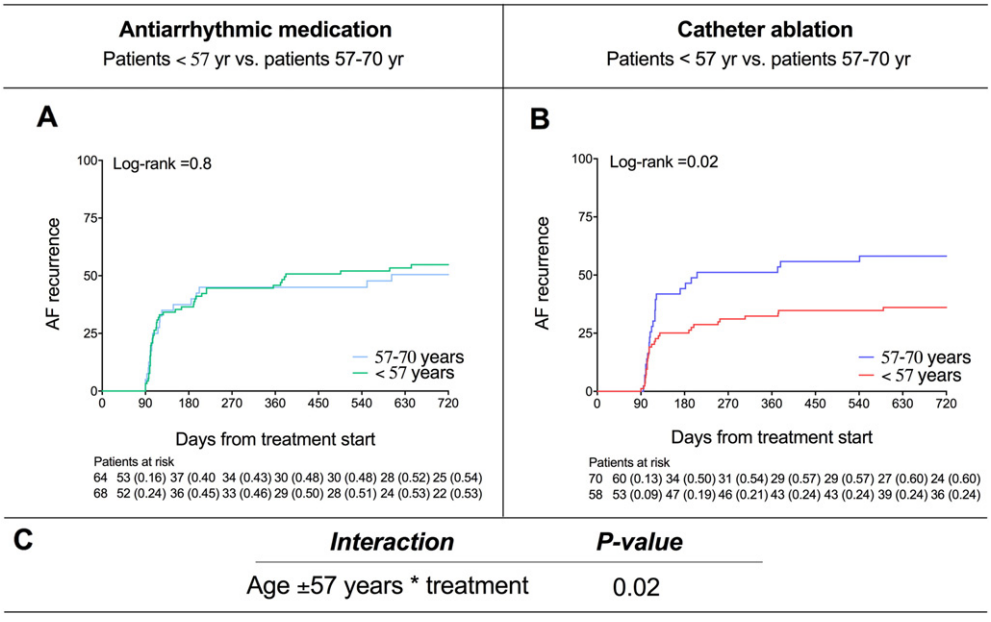

Fig. 1. Kaplan Meier plots of AF recurrence stratified by age <57 years and 57–70 years in patients treated with antiarrhythmic medication (A) and catheter ablation (B) as well as the interaction between age and treatment group (C). Higher age was not associated with risk of AF recurrence in patients treated with antiarrhythmic medication whereas higher age was highly associated with AF recurrence after catheter ablation. Abbreviations: SVEC indicates supraventricular ectopic complexes, AF; atrial fibrillation.

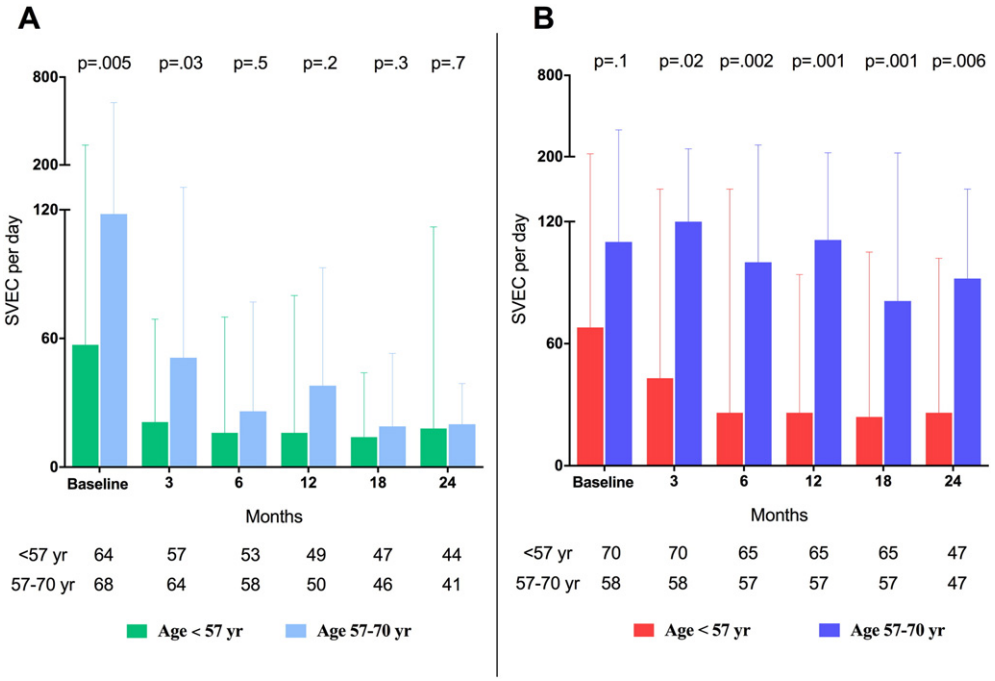

Fig. 2. Supraventricular ectopic complexes in patients aged <57 years and patients 57–70 years after antiarrhythmic medication (A) and catheter ablation (B). The figure shows a comparison of daily burden of supraventricular ectopic complexes in patients <57 years and 57–70 years, respectively as well as between treatment groups within each age group during 24-months of follow-up. The number of patients included is depicted on each column. Abbreviations: SVEC indicates supraventricular ectopic complexes; AF, atrial fibrillation; AAD, antiarrhythmic medication; CA, catheter ablation; yr, years.

comparison, SVEC burden decreased in both age groups after antiarrhythmic medication.

We further investigated the risk of AF recurrence associated with higher SVEC burden at 3 months of follow-up. High SVEC burden was associated with higher risk of AF recurrence after catheter ablation in patients 57–70 years (HR 3.1 [1.4–7.9], $p = 0.005$), but not in younger patients: (HR 2.0 [0.9–4.3], $p = 0.09$). This difference was not found in patients treated with antiarrhythmic medication (<57 years: HR 5.2 [2.7–10.0], $p < 0.0001$ vs 57–70 years: HR 8,5 [3.3–21.7], $p < 0.0001$, $p = 0.04$ for interaction).

3.4. Comorbidity and AF recurrence

Higher age and use of beta-blockers were associated with AF recurrence in patients <57 years treated with catheter ablation. In older patients treated with catheter ablation only high SVEC burden was associated with risk of AF recurrence. No other patient characteristics or comorbidities were associated with AF recurrence in patients treated with antiarrhythmic medication (Supplemental appendix, Tables S1 and S2).

After adjustment for age, hypertension, left atrial diameter and use of beta-blockers, use of beta-blockers and age but not SVEC burden were associated with AF recurrence in patients <57 years treated with catheter ablation (beta-blockers: HR 3.0 [1.0–8.8], $p = 0.04$, age: HR 1.1 [1.0–1.2]. $p = 0.008$). In patients aged 57–70 years only high SVEC burden was associated with AF recurrence after adjustment (>195 SVEC: HR 3.4 [1.4–7.9], $p = 0.005$). In the antiarrhythmic medication group, high SVEC burden remained highly associated with AF recurrence in both age groups (<57 years and >195 SVEC: HR 5.9 [3.0–11.8], $p < 0.0001$ vs 57–70 years and >195 SVEC: HR 14.8 [4.5–45.8], $p < 0.0001$) after adjustment for age, hypertension, left atrial diameter and use of beta-blockers.

3.5. Sensitivity and specificity

The sensitivity and specificity of a cut-off of >195 SVEC/day in the overall population were 61% and 75%, respectively. In the AAD group, the positive predictive value (PPV) and negative predictive value (NPV) were 80% and 72% for patients <57 years and 77% and 68% for patients 57–70 years. After catheter ablation, the PPV and NPV were 77% and 59% in patients <57 years and 72% and 75% in patients 57–70 years. The diagnostic optimum is in Supplemental appendix (Table S3).

4. Discussion

4.1. Major findings

The principal findings of the study are that younger patients undergoing catheter ablation have a significant lower AF recurrence rate as compared to older patients and that higher age was associated with higher post-procedural SVEC burden after catheter ablation. We further observed that high SVEC burden was strongly associated with AF recurrence in older patients undergoing catheter ablation but not in younger patients. These age-related differences were not observed in patients treated with antiarrhythmic medication. Taken together, our findings suggest that younger patients respond differently to catheter ablation.

4.2. Age and SVEC burden

Our research group and others have previously an association between SVEC burden and AF initiation and recurrence [12–16]. To our best knowledge, this study is the first to demonstrate that the association between SVEC burden and AF recurrence after catheter ablation is age-dependent and our data have important clinical implications.

The low recurrence rate and low SVEC burden in younger patients after catheter ablation indicate that the primary triggers of AF are ectopic beats mainly located in the pulmonary veins as originally described by Haissaguere et al. [2]. In younger patients, only use of beta-blockers was predictive of AF recurrence which may be due to more frequent or more sustained AF episodes in these patients and thus more AF recurrence.

The high SVEC burden in older patients may be due to non-pulmonary vein triggers. These findings are in accordance with Santageli et al. who found a high rate of non-pulmonary triggers in octogenarians and hypothesized that older patients have a different underlying pathophysiology of AF [17]. The MANTRA-PAF trial protocol did not include investigation of the substrate during the ablation, hence we can only speculate about the mechanism behind our observations. However, our findings suggest that these age-related changes may extend to patients aged 57–70 years and this could explain the higher SVEC burden and higher recurrence rate after catheter ablation in older patients [18]. Other research groups have found that searching for non-pulmonary triggers in addition to pulmonary vein isolation significantly increases the efficacy of ablation and our results indicate that this may be increasingly important in older patients.

Interestingly, we did not observe a difference in the efficacy of antiarrhythmic medication among patients aged <57 and patients aged 57–70 years. In addition, both age groups treated with antiarrhythmic medication had a high recurrence rate despite a lower SVEC burden. This is also in contradiction to the original results from the MANTRA PAF study where patients treated with antiarrhythmic medication had a higher AF burden. Again, we can only speculate on the cause of these paradoxical findings, but it is possible that only SVECs with a certain timing and origin can trigger AF and that antiarrhythmic medication is not as effective in removing these SVECs.

No other patient characteristics or comorbidities were associated with AF recurrence, however, our study population only included patients younger than 70 years with little comorbidity and without severe left atrial enlargement and unmeasured age-related baseline characteristics may bias the outcome. Even though our result may not be extrapolated to patients >70 years or to patients with more comorbidity, this patient population, who is frequently encountered in clinical practice, in our opinion reflects the segment of patients with paroxysmal AF who most likely would be considered for catheter ablation as first-line treatment. Accordingly, our data add to better understand the impact of age in patients with paroxysmal AF undergoing catheter ablation and suggest new opportunities exist to improve outcome after catheter ablation in older patients with paroxysmal AF.

4.3. Study limitations

The MANTRA PAF study was conducted between 2005 and 2009 prior to the introduction of routine use multipolar catheters to ensure complete electrical isolation of the pulmonary veins and incomplete electrical isolation may have affected our results. Secondly, linear ablation lines were performed at the operator's discretion. However, linear ablation lines can be pro-arrhythmic and thus could bias our results. Furthermore, we used AF episodes ≥1 min as pre-specified in the study protocol [11]. Today, there is consensus that episodes of >30 s should be reported [19].

Presence of AF excludes presence of ectopic complexes which is a potential confounder when categorizing patients according to ectopy burden causing patients with high AF burden to be categorized as patients with few ectopic complexes. However, given that the average AF duration in the population was very low we allowed patients with <100% AF to remain in the analyses. Hence, our study may tend to underestimate the prevalence of SVEC.

Patients randomized and treated with antiarrhythmic medication who subsequently underwent supplementary catheter ablation and patients randomized and treated with catheter ablation who had supplementary antiarrhythmic medication during follow-up were censored at the time of crossover. However, most of these crossovers were in patients treated with antiarrhythmic medication and this could cause bias tending to overestimate the effect of antiarrhythmic medication. Finally, we defined high SVEC burden as the top 75th percentile of the frequency of SVEC which yielded a sensitivity and specificity of 61% and 75%. However, this arbitrarily defined cutoff point needs to prove its value in other populations.

5. Conclusion

We found that younger and older patients respond differently to CA and that SVEC burden was only associated with AF recurrence in older patients treated with catheter ablation.

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Conflicts of interest

Christian Jons, MD, CONSULTANT FEES/HONORARIA - Biotronik.

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No other conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2017.09.208.

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