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Clinical Research

Pulmonary Vein Isolation in Elderly Patients ≥ 75 Years: A Propensity Score-Matched Analysis With Focus on Differences Among Atrial Fibrillation Types

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See editorial by Chew and Morillo, pages 1551-1553 of this issue.

ABSTRACT

Background: Age is a major risk factor for development of atrial fibrillation (AF) and associated with increased recurrence rates in the setting of rhythm control. Current data tend to support catheter ablation in elderly patients, but uncertainties exist regarding efficacy and safety of ablation in elderly patients.

Methods: This was a prospective single-centre observational study with propensity score matching (PSM) to investigate the influence of age on efficacy and safety of cryoballoon ablation (CBA) stratified by age (< 75 years vs ≥ 75 years) and AF phenotype (paroxysmal vs persistent). Primary efficacy endpoint was recurrence of atrial arrhythmia after a 90-day blanking period. Safety endpoints were death, stroke, or procedure-associated complications.

Results: Consecutive patients (n = 953) underwent CBA for first-time AF ablation. Median follow-up was 18 months. By means of PSM, 268 matches were formed. At 1 year, primary efficacy endpoint occurred in

RÉSUMÉ

Contexte : L'âge est un facteur de risque majeur pour le développement de la fibrillation auriculaire (FA) et est associé à des taux de récidive accrus dans le cadre du contrôle du rythme cardiaque. Les données actuelles tendent à encourager l'ablation par cathéter chez les patients âgés, mais des incertitudes subsistent quant à l'efficacité et à la sécurité de l'ablation chez les patients âgés.

Méthodes : Il s'agissait d'une étude observationnelle prospective monocentrique avec appariement sur score de propension (ASP) visant à étudier l'influence de l'âge sur l'efficacité et la sécurité de l'ablation par cryoballon (ACB) stratifiée selon l'âge (< 75 ans vs ≥ 75 ans) et le phénotype de la FA (paroxystique vs persistante). Le critère principal d'efficacité était la récidive de l'arythmie auriculaire après une période de pause de 90 jours. Les critères d'évaluation de la sécurité étaient le décès, l'accident vasculaire cérébral ou les complications associées à la procédure.

Catheter ablation represents the most effective method for rhythm control in patients with atrial fibrillation (AF). In this context, pulmonary vein isolation (PVI) has gained massive value for the initial treatment of symptomatic paroxysmal AF[1,2] but has also been convincing in patients with persistent AF.[3,4] Attempts to reduce the arrhythmia recurrence rate after PVI in persistent AF by means of additional extended ablation such as elimination of complex fractionated electrograms and addition of linear lesions,[5,6] posterior left wall isolation,[7] or magnetic resonance imaging (MRI)-guided fibrosis ablation[8] have largely failed, leaving PVI as the cornerstone of ablation procedures in persistent AF.

Age is a main risk factor for initial development and later progression of AF from paroxysmal to persistent and permanent types[9,10] and has been a predictor of ablation-related complications in some studies,[11,12] resulting in a remaining ambiguity regarding patient safety.[13]

Several previous studies attributing equal efficacy and safety to PVI irrespective of patient age did not differentiate among AF types when reporting patient collectives.[14-22] Only a few studies actually distinguished between paroxysmal[23] and persistent[24,25] AF when comparing younger with older patients. Although it seems that there is no difference in efficacy and safety of catheter ablation between younger and elderly

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22.4% of young vs 33.2% of elderly patients, including both AF phenotypes (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.47-0.90; $P = 0.01$). AF relapse occurred in 19.7% of young vs 28.5% of elderly patients with paroxysmal (HR, 0.63; 95% CI, 0.40-0.99; $P = 0.046$) compared with 25.9% (30 of 116, young) vs 38.8% (45 of 116, elderly) patients with persistent AF (HR, 0.62; 95% CI, 0.39-0.97; $P = 0.038$). No difference was observed regarding the incidence of safety endpoints between young and elderly patients ($P = 0.38$).

Conclusions: CBA is associated with higher recurrence rates in elderly ($\geq$ 75 years) than in younger patients, with highest recurrence rates in elderly patients with persistent AF.

Résultats : Les patients rencontrés consécutivement (n = 953) ont subi une ACB pour une première ablation de la FA. Le suivi médian était de 18 mois. Au travers de l'ASP, 268 correspondances ont été réalisées. À un an, le principal critère d'efficacité a été atteint chez 22,4 % des jeunes patients contre 33,2 % des patients âgés, en incluant les deux phénotypes de FA (rapport de risque [RR], 0,65; intervalle de confiance [IC] à 95 %, 0,47-0,90; $P = 0,01$). Une récidive de la FA s'est produite chez 19,7 % des jeunes patients contre 28,5 % des patients âgés atteints de FA paroxystique (RR, 0,63 ; IC à 95 %, 0,40-0,99 ; $P = 0,046$), et en comparaison, chez 25,9 % (30 jeunes sur 116) contre 38,8 % (45 personnes âgées sur 116) des patients atteints de FA persistante (RR, 0,62 ; IC à 95 %, 0,39-0,97 ; $P = 0,038$). Aucune différence n'a été observée en ce qui concerne l'incidence des critères d'évaluation de la sécurité entre les jeunes patients et les patients âgés ($P = 0,38$).

Conclusions : L'ACB est associée à des taux de récidive plus élevés chez les patients âgés ($\geq$ 75 ans) que chez les patients plus jeunes, avec les taux de récidive les plus élevés étant observés chez les patients âgés présentant une FA persistante.

patients in paroxysmal as well as most mixed populations, there is suspicion for limited efficacy of PVI in elderly with persistent AF.[24,25] Accordingly, we sought to perform a prospective comparison between younger and elderly patients, stratified by AF phenotype.

Methods

Study design, inclusion, and exclusion criteria

Consecutive patients ($\geq$ 18 years of age) undergoing first time cryoballoon ablation (CBA) for symptomatic paroxysmal or persistent AF between January 2018 and December 2022, at St Josefs-Hospital Wiesbaden (Germany) were prospectively enrolled in this observational single-centre study. Exclusion criteria were contraindication to CBA, including the presence of atrial thrombus, repeat PVI, and inability to consent. Patient characteristics were collected at time of enrollment. The analysis was approved by the regional ethics committee (Landesaerztekammer Hessen) and carried out in accordance with the Declaration of Helsinki.

Efficacy and safety endpoints

Primary efficacy endpoint was defined as first documented recurrence of clinical AF, atrial flutter, or atrial tachycardia after a 90-day blanking period following CBA. In accordance with the current European Society of Cardiology (ESC) guidelines on AF,[13] the diagnosis of clinical AF/atrial arrhythmia was based on 12-lead electrocardiogram (ECG) recording or a single-lead ECG showing $\geq$ 30 seconds of arrhythmia The primary safety endpoint consisted of death from any cause or stroke or transient ischemic attack and procedure-related complications including death, major groin-site complications requiring treatment, and prolonging hospitalization, pericardial tamponade and effusion, cerebrovascular or systemic embolism, and phrenic nerve injury. In addition, total procedure time, left-atrial (LA) dwell time, fluoroscopy time, use of contrast dye, and radiation dose were analyzed.

Ablation procedure

Our standardized procedure flow has already been described in detail.[26] In brief, after anatomically guided femoral vein puncture, a steerable 15-F sheath (FlexCath Advance, Medtronic, Minneapolis, Minnesota, USA) was inserted into the LA following fluoroscopically guided transseptal puncture (TSP) after administration of 5000 units of unfractionated heparin before TSP. Administration of oral non-vitamin K antagonists was paused on the morning of CBA, and an activated clotting time of 300 to 350 seconds was targeted during the procedure. The second-generation (Arctic Front, Medtronic) 28-mm balloon was introduced, inflated in the LA, and advanced to the ostium of each pulmonary vein. Pulmonary vein signals were recorded with an octapolar, circular mapping catheter (Achieve, Medtronic), and occlusion of pulmonary veins was assessed with venous angiography.

CBA was performed with freeze duration of 180 seconds per pulmonary vein. When visualized online, time to isolation +120 seconds was used as dosing protocol. In veins without reliable signals one 180-second freeze was applied and isolation confirmed by absence of signals or capture. Ablation of right-sided veins was performed under phrenic nerve stimulation with a decapolar catheter (Dynamic, Boston Scientific, Marlborough, Massachusetts, USA). All veins were rechecked at the end of the procedure.

Procedures were performed under propofol sedation. Propofol infusion was terminated before isolation of the last pulmonary vein to allow short sedation times. Class I and III antiarrhythmic drugs (AADs) were discontinued at the end of the 90-day blanking period, and oral anticoagulation was performed according to the CHA_2DS_2-VASc score, as per guidelines.

Follow-up

Follow-up was aimed at detecting clinical recurrence of atrial arrhythmias and safety endpoints. Follow-up was based on predefined systematic telephone interviews after 3, 6, 12, 18, 24, and 36 months and included a query

Table 1. Baseline characteristics according to age and AF type

Characteristic	Paroxysmal AF (n = 581)			Persistent AF (n = 372)		
	< 75 years (n = 395)	≥ 75 years (n = 186)	*P*	< 75 years (n = 242)	≥ 75 years (n = 130)	*P*
Age (years)	64.1 ± 8.0	80.1 ± 3.2	< 0.001	63.9 ± 8.5	79.9 ± 3.1	< 0.001
Female sex	150 (38%)	110 (59%)	< 0.001	82 (34%)	73 (56%)	< 0.001
BMI (kg/m^2)	28.4 ± 6.8	26.3 ± 4.1	< 0.001	28.4 ± 4.8	26.0 ± 4.0	< 0.001
Antiarrhythmic drugs (during/after blanking period)						
Overall	66 (17%)/32 (9%)	37 (20%)/30 (16%)	0.35/0.64	64 (26%)/30 (12%)	30 (23%)/14 (11%)	0.48/0.36
Flecainide	43 (11%)/26 (7%)	12 (6%)-12 (6%)	0.09/0.95	28 (12%)/18 (7%)	11 (8%)-2 (2%)	0.35/0.02
Amiodarone	23 (6%)/6 (2%)	24 (13%)-18 (10%)	0.004/< 0.001	36 (15%)/11 (5%)	18 (14%)-12 (9%)	0.79/0.07
Dronedarone	0 (0%)/0 (0%)	1 (1%)-0 (0%)	0.14/ -	0 (0%)/ 1 (0%)	1 (1%)-0 (0%)	0.17/0.46
CHA_2DS_2-VASc score	2.1 ± 1.3	4.1 ± 1.1	< 0.001	2.2 ± 1.3	3.9 ± 1.2	< 0.001
LA diameter (mm)	41 ± 8	43 ± 9	< 0.001	43 ± 9	44 ± 9	< 0.001
HFrEF (LVEF ≤ 40%)	35 (9%)	17 (9%)	0.91	45 (19%)	25 (19%)	0.88
Coronary artery disease	63 (16%)	60 (32%)	< 0.001	32 (13%)	37 (28%)	< 0.001
Hypertension	228 (58%)	149 (80%)	< 0.001	158 (66%)	101 (78%)	0.01
Hyperlipidemia	61 (15%)	31 (17%)	0.71	35 (15%)	20 (15%)	0.81
Diabetes	43 (11%)	31 (17%)	0.05	24 (10%)	15 (12%)	0.63
Impaired renal function (GFR < 60 mL/min)	58 (15%)	91 (49%)	< 0.001	35 (14%)	42 (32%)	< 0.001
Previous stroke	27 (7%)	15 (8%)	0.59	8 (3%)	13 (10%)	0.008

Continuous data are presented as mean value ± standard deviation, numbers and percentage (in brackets) are given for absolute values; 90-day blanking period.
AF, atrial fibrillation; BMI, body mass index; GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; LA, left atrial; LVEF, left ventricular ejection fraction.

regarding detection of or rehospitalization because of atrial arrhythmia as well as the occurrence of the safety endpoints described here. Patients were instructed to visit either their cardiologist or our outpatient clinic to record a 12-lead ECG 3 months after CBA and every 6 months thereafter or whenever symptoms suggestive of atrial arrhythmia occurred. ECGs with suspected arrhythmia recurrence were requested and analyzed by an electrophysiologist at our centre.

Statistical analysis

Only patients with at least 12-month follow-up were included in the analysis. Patient characteristics and procedure parameters were tested for normal distribution. Normally distributed variables were compared using 2-sample Student's *t*-test and are presented as mean and standard deviation. Dichotomous variables were compared using the χ^2 test. Cox-regression analysis was performed to analyze the influence of patient characteristics on recurrence of atrial arrhythmia as primary efficacy outcome. Linear and spline regression were used to evaluate the association between primary efficacy endpoint and age.

Age groups were matched by propensity scores in a 1:1 ratio. Propensity scores for belonging to age groups (< 75 or ≥ 75 years) were calculated by a logistic regression model with AF phenotype (paroxysmal, persistent), sex, body mass index (BMI), impaired renal function, LA diameter, heart failure with reduced ejection fraction (HFrEF), presence of arterial hypertension, diabetes, coronary artery disease, stroke, and intake of any antiarrhythmic medication as the independent variables. Age groups were matched in a 1:1 ratio with a caliper of 0.3 with exact matching for AF type.

The Kaplan-Meier method was used to calculate event-rate estimates. Significance level was set at 0.05. Statistical analyses were performed using SPSS version 28 (IBM, Armonk, New York, USA), R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and PRISM software version 10.0.1 (GraphPad, San Diego, California, USA).

Results

Patient population

A total of 953 consecutive patients with symptomatic AF were enrolled and underwent at least 12-month follow-up after CBA. Of these, 581 (61%) had paroxysmal and 372 (39%) had persistent AF; 316 patients (33%) were elderly (≥ 75 years), and 637 patients (67%) were < 75 years. Median follow-up was 18 months.

Baseline characteristics of patients < 75 and ≥ 75 years of age stratified by AF type are illustrated in Table 1. Elderly patients were significantly more often female; had lower BMI; higher CHA_2DS_2-VASc score; larger LA diameter; and higher prevalence of coronary artery disease, arterial hypertension, and HFrEF, regardless of AF phenotype. Elderly patients with paroxysmal AF were also more likely to have diabetes, whereas elderly patients with persistent AF were more likely to have history of stroke. The overall rate of antiarrhythmic medication during and

Table 2. Influence of clinical characteristics on primary efficacy endpoint in paroxysmal and persistent AF (Cox-regression model)

	Paroxysmal AF						Persistent AF					
	Univariate Cox regression			Multivariate Cox regression			Univariate Cox regression			Multivariate Cox regression		
	P	Exp (B)	95% CI	*P*	Exp (B)	95% CI	*P*	Exp (B)	95% CI	*P*	Exp (B)	95% CI
Age	0.001	1.03	1.01-1.04	0.001	1.03	1.01-1.04	< 0.001	1.04	1.02-1.06	< 0.001	1.04	1.02-1.06
Female sex	0.16	0.83	0.63-1.08				0.01	0.67	0.49-0.91	0.27	0.84	0.61-1.15
BMI (kg/m^2)	0.80	1.00	0.98-1.03				0.047	0.97	0.93-1.00	0.52	0.99	0.95-1.03
LA diameter	0.048	1.02	1.00-1.03	0.25	1.01	0.99-1.03	0.68	0.99	0.98-1.01			
HFrEF (LVEF ≤ 40%)	0.36	1.23	0.79-1.94				0.05	0.65	0.42-1.00	0.07	0.66	0.43-1.03
Coronary artery disease	0.59	1.09	0.79-1.51				0.662	1.09	0.74-1.60			
Hypertension	0.94	1.01	0.76-1.34				0.89	1.02	0.73-1.43			
Hyperlipidemia	0.76	1.06	0.74-1.52				0.75	0.93	0.61-1.44			
Diabetes	0.29	1.24	0.84-1.83				0.13	0.65	0.37- 1.14			
Impaired renal function (GFR < 60 mL/min)	0.76		0.77-1.43				0.04	1.44	1.01-2.05	0.52	1.13	0.78− 1.64
Previous stroke	0.28	0.73	0.41-1.30				0.72	1.12	0.61-2.06			

AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; LA, left atrial; LVEF, left ventricular ejection fraction.

after 90-day blanking period was approximately the same in all age and AF groups.

Association of clinical characteristics and type of AF with recurrence of atrial arrhythmia

Table 2 presents the outcome of univariate and multivariate Cox-regression analysis. Multivariate analysis was performed by forced entry using the characteristics that were statistically significant in univariate analysis.

By means of univariate regression analysis, in patients with paroxysmal AF, older age and LA diameter were associated with a higher rate of recurrence of atrial arrhythmia. In patients with persistent AF, univariate analysis showed an association between higher recurrence rate of atrial arrhythmia and older age, female sex, lower BMI, HFrEF, and impaired renal function. However, after adjustment, in the multivariate analysis, only age was significantly associated with an increased recurrence of atrial arrhythmias in patients with both paroxysmal and persistent AF (Table 2).

Linear and spline regression were used to examine the relationship between age and occurrence of the primary efficacy endpoint at 12 months. A significant linear relationship was found for both paroxysmal ($P < 0.001$) and persistent ($P < 0.001$) AF, whereas spline regression was nonsignificant for both paroxysmal ($P > 0.3$) and persistent ($P > 0.3$) AF (Fig. 1). This implies that no "cutoff age" exists from which the rate of recurrence of arrhythmia increases abruptly, but that there is rather a steady linear increase in rate of recurrence

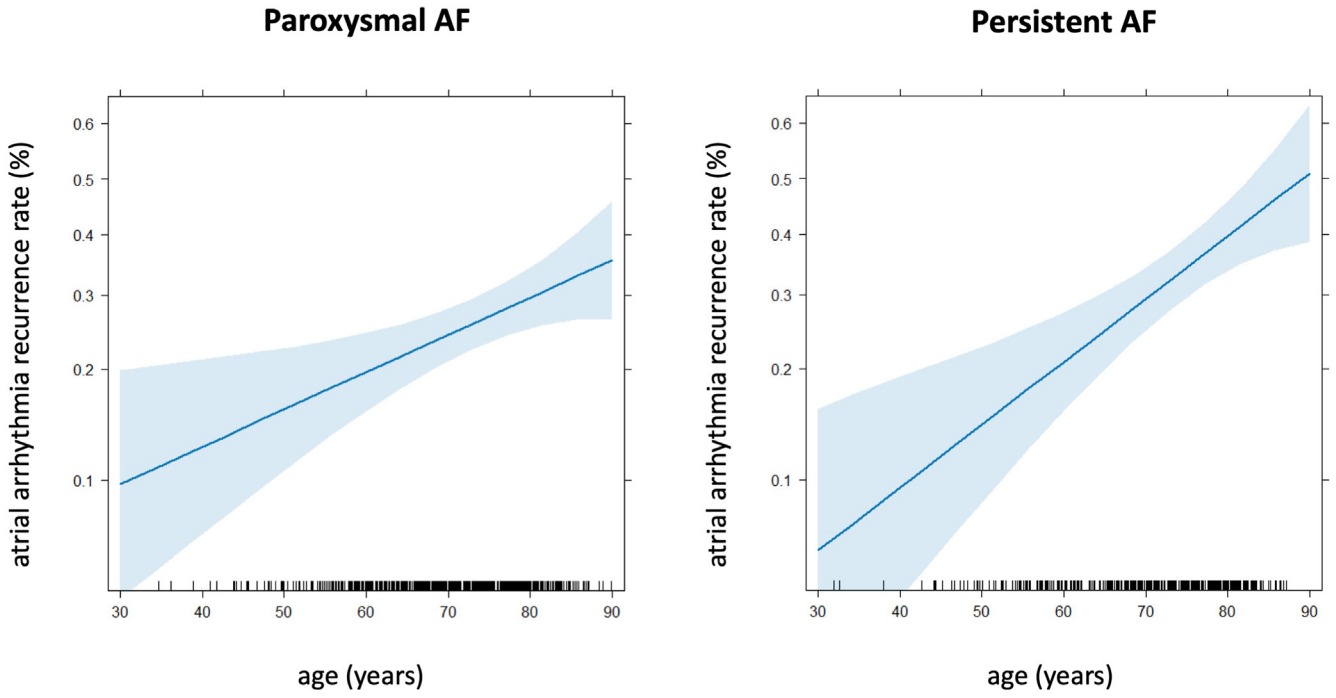

Figure 1. Linear correlation between age and 12-month atrial arrhythmia recurrence rate following cryoballoon pulmonary vein isolation for paroxysmal and persistent atrial fibrillation.

Table 3. Baseline characteristics according to age after propensity score matching

Characteristic	< 75 years (n = 268)	≥ 75 years (n = 268)	*P*
Age (years)	69.2 ± 10.2	79.9 ± 3.2	< 0.001
Male sex	133 (50%)	122 (46%)	0.34
Persistent AF	116 (43%)	116 (43%)	> 0.99
BMI (kg/m^2)	26.9 ± 4.8	26.5 ± 4.0	0.42
Antiarrhythmic drugs (during/after blanking period)			
Overall	54 (20%)/28 (10%)	57 (21%)-34 (13%)	0.75/0.42
Flecainide	21 (8%)/19 (7%)	21 (8%)-13 (5%)	> 0.99/0.27
Amiodarone	33 (12%)/9 (3%)	35 (13%)-21 (8%)	0.80/0.02
Dronedarone	0 (0%)/0 (0%)	1 (0%)-0 (0%)	0.32/ -
CHA_2DS_2-VASc score	2.8 ± 1.5	3.9 ± 1.1	
LA diameter (mm)	43 ± 8	44 ± 10	0.39
HFrEF (LVEF ≤ 40%)	40 (15%)	33 (12%)	0.38
Coronary artery disease	68 (25%)	69 (26%)	0.92
Hypertension	191 (71%)	204 (76%)	0.20
Hyperlipidemia	41 (15%)	39 (15%)	0.81
Diabetes	37 (14%)	34 (13%)	0.70
Impaired renal function (GFR < 60 mL/min)	71 (26%)	95 (35%)	0.03
Previous stroke	22 (8%)	25 (9%)	0.65

Continuous data are presented as mean value ± standard deviation; numbers and percentage (in brackets) are given for absolute values; 90-day blanking period.
AF, atrial fibrillation; BMI, body mass index; GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; LA, left atrial; LVEF, left ventricular ejection fraction.

with increasing age, irrespective of AF type. Against this background, a pragmatic approach with a cutoff of ≥ 75 years of age for the definition of elderly patients was chosen for further analysis.

Propensity-score matching and occurrence of efficacy and safety endpoints

To maximize comparability between younger (< 75 years) and elderly (≥ 75 years) patients, age groups were matched by propensity scores in a 1:1 ratio, with exact matching for AF type. Propensity scores included AF type; sex; BMI; impaired renal function; LA diameter; HFrEF; and presence of arterial hypertension, diabetes, coronary artery disease, stroke, and intake of any antiarrhythmic medication. A total of 268 matched pairs (152 with paroxysmal and 116 with persistent AF, equating to 536 patients in total) could thus be formed (Table 3).

In the overall matched population (containing both AF phenotypes), the primary efficacy endpoint occurred in 22.4% (60 of 268) of young vs 33.2% (80 of 268) of elderly patients at 1 year (1-year Kaplan-Meier event rate estimates: hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.47-0.90; $P = 0.01$) and in 36.2% (97 of 268) of young vs 50.0% (134 of 268) of elderly patients at maximum follow-up (3-year Kaplan-Meier event rate estimates: HR, 0.65; 95% CI, 0.50-0.84; $P = 0.001$; Fig. 2A).

In paroxysmal AF, the primary efficacy endpoint occurred in 19.7% (30 of 152) of young vs 28.5% (43 of 152) of elderly patients at 1 year (HR, 0.63; 95% CI, 0.40-0.99; $P = 0.046$) and in 32.9% (50 of 152) of young vs 42.4% (64 of 152) of elderly patients at maximum follow-up (3-year Kaplan-Meier event-rate estimates: HR, 0.69; 95% CI, 0.48-0.99; $P = 0.045$; Fig. 2B).

In persistent AF, the primary efficacy endpoint occurred in 25.9% (30 of 116) of young vs 38.8% (45 of 116) of elderly patients at 1 year (HR, 0.62; 95% CI, 0.39-0.97; $P = 0.038$) and in 40.5% (47 of 116) of young vs 59.6% (69 of 116) of elderly patients at maximum follow-up (3-year Kaplan-Meier event-rate estimates: HR, 0.55; 95% CI, 0.38-0.80; $P = 0.001$; Fig 2C).

The incidence of safety endpoints in the matched cohort was low throughout the follow-up period. A total of 22 safety endpoints occurred (4.1% of all procedures). Of these, 9 (3.4%) occurred in young and 13 (4.9%) in elderly patients ($P = 0.38$) with the higher number of events primarily because of more noncardiovascular deaths in patients ≥ 75 years (Table 4).

Safety endpoints were similarly distributed between patients with paroxysmal (13 endpoints, 4.3%) and persistent AF (9 endpoints, 3.9%). There was no difference in the occurrence of safety endpoints between younger and older patients with paroxysmal ($P = 0.16$) or between younger and elderly patients with persistent AF ($P = 0.73$). The exact distribution of endpoints is shown in Table 4.

Procedural parameters

In paroxysmal AF, there was no difference in total procedure time (51 ± 14 minutes vs 53 ± 15 minutes; $P = 0.50$), LA dwell time (35 ± 14 minutes vs 33 ± 12 minutes; $P = 0.20$), fluoroscopy time (6.8 ± 3.2 minutes vs 6.9 ± 3.3 minutes; $P = 0.82$), use of contrast dye (46 ± 34 mL vs 42 ± 34 mL; $P = 0.32$), and radiation dose (269 ± 252 cGy*cm^2 vs 262 ± 189 cGy*cm^2; $P = 0.80$) between younger and elderly patients.

Similarly, in persistent AF, no differences concerning total procedure time (55 ± 17 minutes vs 52 ± 15 minutes; $P = 0.18$), LA dwell time (37 ± 14 minutes vs 34 ± 13 minutes; $P = 0.15$), fluoroscopy time (7.1 ± 3.7 minutes vs 7.0 ± 3.3 minutes, $P = 0.77$), use of contrast dye (42 ± 32 mL vs 36 ± 31 mL; $P = 0.15$), and radiation dose (356 ± 628 cGy*cm^2 vs 311 ± 420 cGy*cm^2; $P = 0.53$) were observed.

Discussion

This prospective observational study analyzed efficacy and safety of CBA for first PVI in a large propensity score-matched

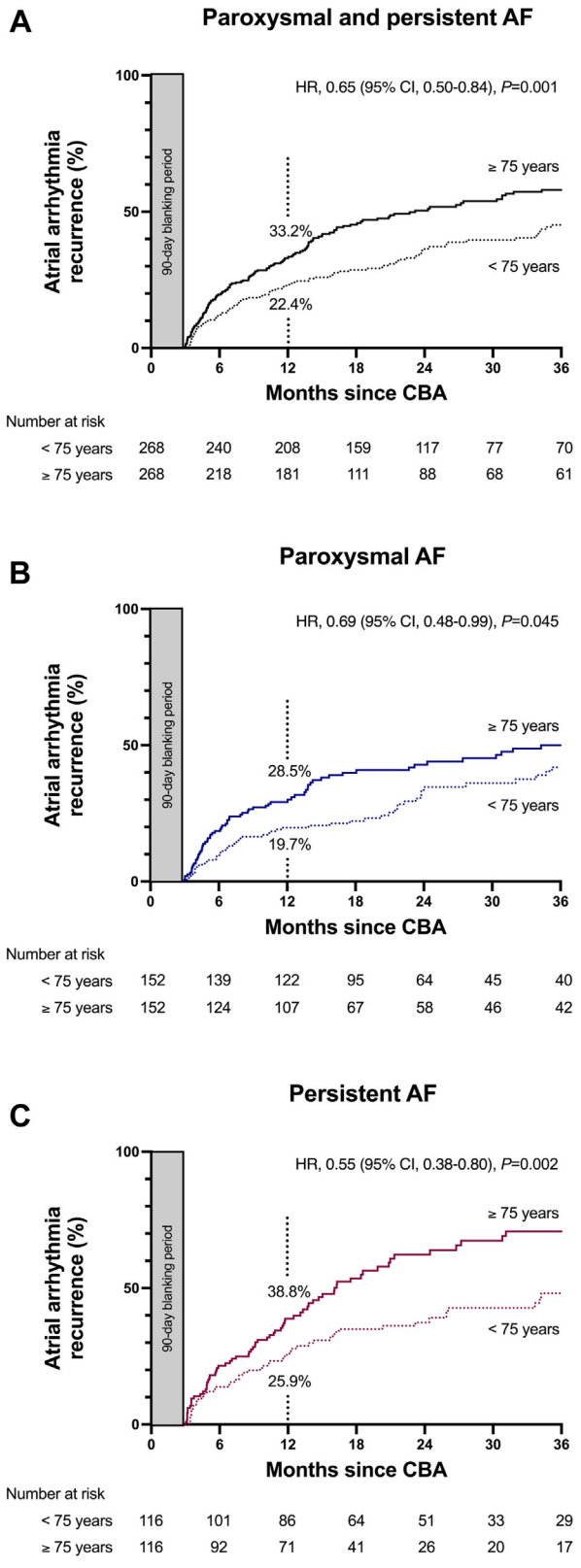

Figure 2. Comparison of young (**dotted line**) and elderly (**continuous line**) patients in the overall propensity score-matched cohort (**1A**, **black**), in patients with paroxysmal (**1B**, **blue**), and persistent (1C, **purple**) AF. AF, atrial fibrillation; CBA, cryoballoon ablation; CI, confidence interval; HR, hazard ratio.

cohort with a focus on age and AF phenotype. It had several key findings:

- Age is the only independent predictor of arrhythmia recurrence after PVI for both paroxysmal and persistent AF.
- There was a linear relationship between increasing age and rate of recurrence after PVI.
- Elderly patients ($\geq$ 75 years) had significantly higher rates of recurrence of arrhythmias than younger patients ($<$ 75 years), regardless of type of AF.
- Elderly patients with persistent AF had the highest rates of recurrence of all patients ($\sim$60% at median follow-up of 18 months).
- There was no difference in occurrence of safety endpoint between young (3.4%) and elderly patients (4.9%).

Definition of "elderly" in this study

The currently used cutoff of $\geq$ 75 years is consistent with the current literature on this topic, in which an age of $\geq$ 75 years has been commonly used to define elderly patients and to examine differences in the efficacy and safety of catheter ablation compared with younger patients. There is no valid definition by Western geriatric societies of the "elderly patient." However, British, Italian, and Japanese[27] geriatric societies increasingly advocate that elderly patients should be defined as 75 years of age or older.[27]

Efficacy and safety of PVI in elderly patients

Early randomized controlled trials of PVI for AF ablation excluded patients $\geq$ 75 years of age,[28-30] and most recent prospective trials on catheter ablation do provide information on elderly patients.[1-4] However, the **E**arly Treatment of **A**trial Fibrillation for **S**troke Prevention **T**rial (EAST-AFNET 4) and **C**atheter **Ab**lation vs **An**ti-Arrhythmic Drug Therapy for **A**trial Fibrillation (CABANA) trial have reported data on efficacy of catheter ablation in patients $\geq$ 75 years (representing $\sim$30% of all patients in EAST-AFNET 4 and 14% in CABANA). Although Eckardt et al., in a prespecified subanalysis of the EAST-AFNET 4 study, showed an increase in the incidence of the primary endpoint (composed of death from cardiovascular causes, stroke, or hospitalization with worsening heart failure or acute coronary syndrome) by more than 50% per 10-year increase in age,[31] Bahnson et al.[32] reported a higher incidence of the primary endpoint (death, disabling stroke, major bleeding, and cardiac arrest) in older patients with catheter ablation than with antiarrhythmic drug therapy in a subanalysis of the CABANA trial.

Still, different studies have addressed catheter ablation, particularly in elderly patients, and reported varying rates of success with different treatment regimens.[14-21,23-25] Except for a very limited number of studies that distinguished between paroxysmal[23] and persistent AF[25,33] when comparing efficacy and safety of catheter ablation, most of the studies available contained mixed populations.[14-21] Given the substantial difference in patient characteristics and comorbidities between patients with paroxysmal and persistent AF (Table 1), it

Table 4. Safety endpoints depending on atrial fibrillation type and age

	Paroxysmal AF		Persistent AF	
	< 75 years n = 152	≥ 75 years n = 152	< 75 years n = 116	≥ 75 years n = 116
Death from any cause	1 (0.7%)	4 (2.6%)	2 (1.7%)	2 (1.7%)
Cardiovascular	–	1 (0.7%)	–	–
Noncardiovascular	1 (0.7%)	3 (2.0%)	2 (1.7%)	2 (1.7%)
Stroke/TIA	2 (1.3%)	2 (1.3%)	1 (0.9%)	1 (0.9%)
Pericardial effusion	–	1 (0.7%)	1 (0.9%)	–
Transient phrenic nerve palsy	1 (0.7%)	2 (1.3%)	–	–
Major groin site complication	–	–	1 (0.9%)	1 (0.9%)
Air embolism into right coronary artery	–	–		–
Total number of safety endpoints	4 (2.6%)	9 (5.9%)	5 (4.3%)	4 (3.4%)

AF, atrial fibrillation; TIA, transient ischemic attack.

becomes apparent that these patient collectives should be analyzed separately.

The majority of studies comparing younger and older patients conclude that PVI is equally effective in elderly patients. In a direct comparison of patients older and younger than 75 years of age, Abugattas et al.[23] reported a rate of recurrence of arrhythmia (at 1 year) of 19% vs 15% (paroxysmal AF collective); Tscholl et al.[21] of 30% vs 25% (mixed collective regarding AF type); and Heeger et al.[17] of 20% vs 18% (mixed collective). However, Bulava et al.[22] and Vermeersch et al.[25] reported higher rates of recurrence in elderly patients with persistent AF (Bulava et al. 41% vs 19% and Vermeersch et al. 69% vs 53% at median follow-up of 2 years; $P < 0.05$). Notably, the latter studies are consistent with our findings showing increased 1-year rates of recurrence in elderly patients with both paroxysmal (29% vs 20%) and persistent AF (39% vs 26%) and the highest recurrence rates in elderly patients with persistent AF. Overall, the reported recurrence rates of previous smaller studies are consistent with our efficacy results, and the occurrence of safety endpoints in our study (4.1%) was also comparable with previous trials reporting data on CBA in elderly patients.[17,21,34] One reason for the significantly higher rate of recurrence of arrhythmias in patients ≥ 75 years may be the substantially larger case number and prospective design with systematic follow-up in the current study.

As our results show that the rate of recurrence following CBA increases linearly with age, no cutoff can be set at which PVI may no longer be indicated. Instead, a pragmatic-based approach seems reasonable.

Source of energy for ablation

The cryoballoon is designed to perform PVI only but may offer several advantages such as freeze-mediated catheter adhesion, facilitating catheter stability; more homogeneous lesions compared with radiofrequency ablation (RFA), potentially forming less new arrhythmogenic tissue and thus reducing the occurrence of LA tachycardia,[28,35] repeat ablation procedures, and cardiovascular rehospitalizations.[36] In addition there is evidence of significantly lower incidence of postprocedural LA thrombi[37] and silent cerebral infarction[38,39] as well as ablation of a relevant part of the pulmonary vein antrum and posterior wall when using a 28-mm balloon.[40]

RFA, on the other hand, can be used to ablate nonpulmonary vein triggers in a focused manner. Santangelli et al.[41] found a significantly higher rate of nonpulmonary vein triggers in elderly patients in their mixed AF type collective and performed additional isolation of the posterior box and ablation of complex electrograms in all patients with persistent AF.[41] However, additional extended ablation such as elimination of complex fractionated electrograms and addition of linear lesions[5,6], posterior left wall isolation[7] or MRI-guided fibrosis ablation[8] have failed in reducing atrial arrhythmia recurrences, making PVI alone the cornerstone of all ablation procedures in persistent AF as well. Nonetheless, an argument in favour of RFA is the evidence of reduced progression from paroxysmal to persistent AF with contact-force–guided RFA compared with CBA.[42] An analysis comparing RFA and CBA in elderly does not exist. It is therefore important to state that our results are only valid in the context of catheter ablation using a cryoballoon. Results of contact-force–guided RFA and pulsed-field ablation in this patient cohort must be awaited.[43]

Alternative therapeutic strategies for elderly patients with symptomatic persistent AF

In view of epidemiologic developments in aging societies, strategies for the treatment of elderly patients with AF need to be developed. This may be especially true for elderly patients with persistent AF who appear to be at highest risk of arrhythmia recurrence among all patients with AF. More extensive ablation techniques for persistent AF, such as ablation of complex fractionated electrograms and addition of linear lesions,[5,6] posterior left-wall isolation,[7] or MRI-guided fibrosis ablation[8] have not been convincing in any randomized trial and do not seem to be an advantageous strategy at present. Considering age and life expectancy, pacemaker implantation and atrioventricular-node ablation might represent a reasonable treatment option.[44] This approach already demonstrated significant reduction in rehospitalization and increase in quality of life in a mixed AF populations,[45,46] significantly reduced all-cause and cardiovascular mortality compared with drug rate control in a propensity score-matched analysis[47] and is currently being studied in ≥ 75-year-old patients in the ongoing prospective randomized Pulmonary-vein Isolation or Ablation of Atrioventricular-node and Pacemaker Implantation for Elderly Patients With Persistent Atrial Fibrillation (ABLATE vs PACE) trial (NCT04906668).

Limitations

In this observational study, a standardized treatment procedure was performed by 2 experienced electrophysiologists

(B.M.K. and J.R.E.) in a large study sample. The comparison of patients with different baseline clinical characteristics—for example, patients with paroxysmal and persistent AF or young and elderly patients—makes a direct comparison of a treatment modality vulnerable to confounders but represents observation and analysis under real-world conditions of differently old and comorbid patients. Accordingly, propensity score matching was used to circumvent this limitation.

Follow-up was largely based on telephone interviews aimed at obtaining information regarding detection of or rehospitalization because of atrial arrhythmia, including results of ECGs either recorded by primary care physicians, cardiologists, or symptom-guided ECGs indicative of recurrence of atrial arrhythmia. The lack of continuous ECG-monitoring and the necessity for patient compliance may have led to a relevant underestimation of (especially asymptomatic) occurrence of primary endpoint and do not allow estimation of the AF burden or information on progression of AF.

In the context of asymptomatic AF, Xiong et al.[48] were unable to detect any correlation between age and rate of asymptomatic AF in a meta-analysis, whereas Boriani et al.[49] demonstrated a significant correlation between older age and asymptomatic AF in the **EUR**O**b**servational **R**esearch **P**rogram-**A**trial **F**ibrillation (EORP-AF) pilot registry, with more than 3119 AF patients (approximately 40% who were asymptomatic).

Regarding our monitoring strategy, some aspects need to be considered: Although the current ESC guidelines on AF still debate on the optimal outcome measure for recording ablation success for AF-related outcome,[13] there are data supporting the assessment of AF burden in all future studies. A subanalysis of the **C**atheter **A**blation vs **S**tandard Conventional **T**herapy in Patients With **Le**ft Ventricular Dysfunction and **A**trial **F**ibrillation (CASTLE-AF) study showed that in patients with HFrEF, an AF burden $< 50\%$ at 6 months after catheter ablation was associated with a significant reduction in the composite endpoint of death and rehospitalization, whereas the mere occurrence of an atrial arrhythmia > 30 seconds was not.[50] Furthermore, it is known that higher AF burden is associated with death and occurrence of thromboembolic events.[51,52] However, there is no precise recommendation for an AF burden threshold or a numerical AF burden reduction that defines success of AF ablation.

Conclusions

Elderly patients (≥ 75 years) had significantly higher rates of recurrence than younger patients, regardless of AF type, with highest rates of recurrence in elderly patients with persistent AF. Alternative therapeutic approaches should be evaluated for this patient population.

Ethics Statement

This work has adhered to relevant ethical guidelines and is in line with the declaration of Helsinki.

Patient Consent

The authors confirm that a patient consent form has been obtained for this article.

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Disclosures

The authors' department is international training centre for cryoballoon ablation. J.R.E. has served as speaker for—and advisor to—Medtronic. The other authors have no conflicts of interest to disclose.

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