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Study Design

Pulmonary Vein Isolation or Pace and Ablate in Elderly Patients With Persistent Atrial Fibrillation (ABLATE Versus PACE)—Rationale, Methods, and Design

Andreas A. Boehmer, MD,[a] Bernhard M. Kaess, MD,[a] Christian Ruckes, PhD,[b] Christian Meyer, MD,[c] Andreas Metzner, MD,[d] Andreas Rillig, MD,[d] Lars Eckardt, MD,[e] Stanley Nattel, MD,[f] and Joachim R. Ehrlich, MD;[a] on behalf of the ABLATE Versus PACE Investigators

[a] *St Josefs-Hospital, Wiesbaden, Germany*

[b] *Interdisciplinary Center for Clinical Trials, University Medical Center, Mainz, Germany*

[c] *Evangelical Hospital, Duesseldorf, Germany*

[d] *University Hospital of Hamburg-Eppendorf, Hamburg, Germany*

[e] *Department of Cardiology II—Electrophysiology, University Hospital Münster, Münster, Germany*

[f] *Montréal Heart Institute, Montréal, Québec, Canada*

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ABSTRACT

Age is a major risk-factor for atrial fibrillation (AF) and associated hospitalisations. With increasing emphasis on rhythm control, pulmonary vein isolation (PVI) is often suggested, even to elderly patients (≥ 75 years of age). Efficacy of PVI aiming at rhythm control is limited in persistent AF. Pacemaker implantation with atrioventricular node (AVN) ablation may represent a reasonable alternative, with the aim of controlling symptoms and improving quality of life in elderly patients. In this investigator-initiated, randomised, multicentre trial, we test the hypothesis that pacemaker implantation and AVN ablation provides

RÉSUMÉ

L'âge est un facteur de risque majeur pour la fibrillation auriculaire (FA) et les hospitalisations associées. L'accent étant mis de plus en plus sur le contrôle du rythme, l'isolement des veines pulmonaires (IVP) est souvent proposé, même aux patients âgés (≥ 75 ans). L'efficacité de l'IVP visant à contrôler le rythme est limitée en cas de FA persistante. L'implantation d'un stimulateur cardiaque avec ablation du nœud auriculo-ventriculaire (NAV) peut représenter une alternative raisonnable, dans le but de contrôler les symptômes et d'améliorer la qualité de vie des patients âgés. Dans cet essai multi-

Increasing age is a major risk factor for development of atrial fibrillation (AF) and its progression from paroxysmal to persistent and permanent types.[1,2] In light of ageing Western populations with increasing life expectancy,[3] the number of patients ≥ 75 years of age with AF is expected to double by 2060.[2] This phenomenon will increase the already high demand for AF therapy[4-6] and represent an administrative and financial burden on health care systems.[6,7] But importantly, this number highlights the problem of AF in the elderly and raises the question of the optimal therapeutic approach to AF in this group of patients.[8]

In accordance with current international guidelines of the European Society of Cardiology (ESC), American College of Cardiology/American Heart Association Joint Committee (ACC/AHA/American College of Chest Physicians [ACCP]/Heart Rhythm Society [HRS]), and Canadian Cardiovascular Society (CCS) both rhythm and rate control represent recommended treatment regimens for symptomatic AF, aiming at either maintenance of sinus rhythm or controlling ventricular rate and accepting AF.[9-11] When deciding whether rhythm or rate control strategy is best to meet the individual patient's needs, various factors such as age, durations and type of AF (paroxysmal vs persistent), and risk factors for arrhythmia recurrence should be carefully considered. The section dealing with elderly patients (≥ 75 years of age) in the current ESC guidelines is brief, and it is

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Corresponding author: Dr Joachim R. Ehrlich, Department of Cardiology, St Josefs-Hospital Wiesbaden, Beethovenstraße 20, 65189 Wiesbaden, Germany. Tel.: +49 611 177 1201.

E-mail: jehrlich@joho.de

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superior symptom control over PVI in elderly patients with symptomatic persistent AF, without any increase in adverse event profile. In the ABLATE Versus PACE (NCT 04906668) prospective open-label superiority trial, 196 elderly patients with normal ejection fraction and symptomatic persistent AF despite guideline-indicated medical therapy will be randomised to either cryoballoon PVI (ABLATE) or dual-chamber pacemaker implantation with subsequent AVN ablation (PACE), and followed for a minimum of 12 months. The primary efficacy outcome is a composite end point of rehospitalisation for atrial arrhythmia or cardiac decompensation/heart failure, (outpatient) electrical cardioversion, or upgrade to cardiac resynchronisation therapy owing to worsening of left ventricular ejection fraction to $\leq$ 35%. Secondary end points include death from any cause, stroke, quality of life, and procedure-related complications. Sample size is designed to achieve 80% power for the primary end point (2-tailed alpha of 5%). ABLATE Versus PACE will determine whether pacemaker implantation and AVN ablation can improve symptom-control in elderly patients with persistent AF over PVI without increasing safety end points.

centrique randomisé, à l'initiative de l'investigateur, nous testons l'hypothèse selon laquelle l'implantation d'un stimulateur cardiaque et l'ablation du NAV chez les patients âgés souffrant de FA symptomatique persistante permettrait un meilleur contrôle des symptômes que l'IVP, sans accroissement du taux de complications. Dans le cadre de l'essai prospectif de supériorité, en ouvert, ABLATE *Versus* PACE (NCT 04906668), 196 patients âgés présentant une fraction d'éjection normale et une FA persistante symptomatique, en dépit d'un traitement médical recommandé par les lignes directrices, seront randomisés pour recevoir soit une IPV par cryoballonnet (ABLATE), soit l'implantation d'un stimulateur cardiaque à double chambre suivie d'une ablation de l'AVN (PACE), et seront suivis pendant au moins 12 mois. Le principal critère d'évaluation est un critère composite de réhospitalisation pour arythmie auriculaire ou décompensation cardiaque/insuffisance cardiaque, cardioversion électrique (en ambulatoire) ou passage à une thérapie de resynchronisation cardiaque en raison d'une aggravation de la fraction d'éjection du ventricule gauche à des valeurs $\leq$ 35 %. Les critères d'évaluation secondaires comprennent le décès, toutes causes confondues, l'accident vasculaire cérébral, la qualité de vie et les complications liées à l'intervention. La taille de l'échantillonnage est conçue pour atteindre une puissance de 80 % pour le critère d'évaluation principal (risque alpha bilatéral de 5 %). L'essai clinique ABLATE *Versus* PACE déterminera si l'implantation d'un stimulateur cardiaque et l'ablation du NAV peuvent améliorer le contrôle des symptômes chez les patients âgés souffrant de FA persistante par rapport à l'IVP, sans accroître les risques liés à la sécurité.

not even dealt with in the ACC/AHA/ACCP/HRS and CCS guidelines.[9-11]

Prognostic benefit can be obtained by early rhythm control[12,13] which is most effectively achieved by pulmonary vein isolation (PVI).[14,15] Well founded data on PVI in elderly patients are limited and suggest increased arrhythmia recurrence rates, particularly in persistent AF.[16,17] Rate control by pacemaker (PM) implantation and ablation of the atrioventricular node (AVN) reduces rehospitalisations and improves quality of life, and may therefore represent a reasonable alternative to PVI in elderly patients who remain symptomatic despite guideline-indicated medical therapy.[18-21]

The Pulmonary Vein Isolation or Pace and Ablate in Elderly Patients With Persistent Atrial Fibrillation trial (ABLATE Versus PACE; 04906668) represents a prospective, multicentre, randomised comparison of the 2 therapeutic concepts (catheter-based rhythm vs rate control) in terms of end points measuring morbidity (such as rehospitalisations, reinterventions, safety, and quality of life) in patients aged 75 years and over.

The aim of this article is to present the background against which the necessity of the ABLATE Versus PACE trial becomes apparent as well as its study methodology.

Rhythm Control by Means of Catheter Ablation (ABLATE)

Several studies have recently demonstrated prognostic benefit (including reduced mortality and rehospitalisations) of rhythm control.[12,22-25] In particular, rhythm control by means of PVI has been more effective than antiarrhythmic drug therapy in preventing atrial arrhythmia recurrence and AF progression.[14,23,26,27] However, frequently overlooked is the fact that the precise contribution of PVI over medical therapy to prognostic benefits in the AF population is currently limited to the subgroup of patients affected by heart failure with reduced ejection fraction (CASTLE-AF, CASTLE-HTx, CABANA).[22,24,28,29] Although rhythm control improved outcome in the EAST-AFNET 4 (Early Rhythm Control Therapy in Patients With Atrial Fibrillation) trial, fewer than 20% of patients underwent PVI, and the use of ablation did not seem to affect the primary outcome.[12,30]

In the context of catheter ablation—based AF therapy, PVI represents the current standard and can be achieved equally effectively and safely (overall complication rate ~ 2%-10%) with the use of either thermal energy (radiofrequency or cryoenergy) or pulsed-field (electroporation) ablation.[14,15,23,31-36] Although the central role and efficacy of a PVI-only approach in paroxysmal AF is undisputed,[14,15,32] attempts to reduce arrhythmia recurrences after PVI in persistent AF by means of additional extended ablation, such as elimination of complex fractionated electrograms and addition of linear lesions,[37,38] posterior left wall isolation,[39,40] and magnetic resonance imaging—guided fibrosis ablation,[41] have largely failed, leaving PVI the cornerstone of ablation also in persistent AF.

After PVI, 1-year freedom from arrhythmia recurrence averages 60%-75%[14,31,33] and rehospitalisation rate for cardiovascular causes is approximately 35%.[42] In most studies, arrhythmia recurrences within the first 3 months (so-called blanking period) are not counted, despite recurrences occurring in around 40%-45% of patients during this period.[43,44] Although recurrences within the blanking period are not necessarily associated with the procedural long-term success, from a patient's perspective, quality of life may be significantly impaired because hospitalisation for cardioversion is needed

regardless of when arrhythmia occurs. Recurrences (even during the first 3 months) may be particularly problematic for elderly patients, who are known to prefer treatment to improve quality of life over treatment to prolong life.[45-47]

Given the growing emphasis and demand for rhythm control, the numbers of ablations have increased significantly around the globe over the past 2 decades,[4-6] and PVI is often advocated for elderly patients (≥ 75 years of age) regardless of AF phenotype.[48-55] It is frequently overlooked that there is a paucity of scientific data to support the use of PVI in elderly patients. Important early catheter ablation trials specifically excluded patients aged ≥ 75 years[31,32,34] or ≥ 80 years .[15,56] Most of the more recent trials without age limitation do not specify ablation outcomes in elderly patients.[14,22,24,35,57] Although the age of patients included in these more recent studies without age restriction averaged from 58 to 70 years, specific data for the influence of age on primary study end points are available only for the EAST-AFNET 4 and CABANA (Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation) studies (Table 1).

The EAST-AFNET 4 study demonstrated a paramount prognostic effect based on early rhythm control by reducing the primary composite end point (death from cardiovascular cause, stroke, or hospitalisation with worsening of heart failure or acute coronary syndrome).[12] In EAST-AFNET 4, only about 30% of patients in the trial were aged ≥ 75 years, and the proportion of elderly individuals receiving ablation therapy was less than 4%.[12,30] In a prespecified subanalysis of EAST-AFNET 4, Eckardt et al. demonstrated that for every 10-year increase in age, primary end point occurrence increased ≥ 50% regardless of therapy.[30]

Following the publication of EAST-AFNET 4, Kim et al. studied the same primary end point occurrence in a retrospective database analysis including 31,220 patients from the Korean National Health Insurance Service and found a significant advantage of early rhythm control in patients < 75 years of age (hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.72-0.88), whereas patients ≥ 75 years of age did not similarly benefit (HR 0.94, 95% CI 0.87-1.03).[58]

In a subgroup analysis of CABANA,[28] which included 14% of patients ≥ 75 years of age, Bahnson et al. found reductions of the primary end point (composed of death, disabling stroke, major bleeding, and cardiac arrest) with ablation mostly in younger patients (< 65 years of age; 3.2% vs 7.8%, adjusted hazard ratio [aHR] 0.57, 95% CI 0.30-1.09), and patients ≥ 75 years of age showed more frequent end point occurrence with catheter ablation than with drug therapy (14.8% vs 9.0%, aHR 1.39, 95% CI 0.75-2.58).[59] In addition, for every 10-year increase in age, the primary end point aHR (ie, less favourable for ablation) increased by an average of 27%.[59]

Nevertheless, several small observational studies comparing efficacy and safety of PVI in elderly patients reported favourable outcomes in patients ≥ 75 or ≥ 80 years of age (Table 2).[48-55] Limitations of these studies include 1) generally small number of patients included, 2) mostly retrospective design, and 3) analysis of populations with mixed AF phenotypes (paroxysmal and persistent AF). In contrast, studies in patients with persistent AF have shown higher recurrence rates in patients ≥ 75 years of age.[17,48,60-62] A recent meta-analysis including 19 studies showed a significantly higher arrhythmia recurrence rate and incidence of procedural complications in patients ≥ 75 years of age undergoing first-time catheter ablation.[63]

Limited efficacy of PVI in terms of sinus rhythm maintenance, coupled with an increased incidence of safety end points and failure to reduce adverse cardiovascular end points, raises the question of whether PVI really represents the optimal interventional treatment strategy in patients ≥ 75 years of age, particularly those with persistent AF, or whether alternative therapeutic strategies should be considered.

Rate Control by Pacemaker Implantation and AVN Ablation (PACE)

AVN ablation is presently an accepted option to control ventricular rate in patients unresponsive or intolerant to rate and rhythm control therapy, accepting that these patients will become PM dependent.[9]

PACE strategy is the most effective means of rate control because the ventricular rate is determined purely by the PM,

Table 1. Mean age of patients in trials on catheter ablation for atrial fibrillation (AF) therapy without age restriction

Author	Year	Trial	Comparison	No. of patients enrolled	No. of patients aged ≥ 75 y (%)	Age, mean (range) or ± SD
Marrouche et al.[22]	2018	CASTLE-AF	Catheter ablation vs antiarrhythmic drug therapy	398	NR	64 (56-71) vs 64 (56-74)
Su et al.[35]	2020	STOP Persistent AF	Cryoballoon-PVI for persistent AF (no comparator)	186	NR	65 ± 9
Kirchhof et al.[12]	2020	EAST-AFNET 4	Early rhythm control vs usual care	2517	812 (29) vs 54 (3.9)*	70 ± 8 vs 70 ± 8
Andrade et al.[14]	2021	EARLY-AF	Cryoballon-PVI vs antiarrhythmic drug therapy	303	NR	58 ± 12 vs 60 ± 11
Packer et al.[28]	2021	CABANA	Catheter ablation vs drug therapy (including rate and rhythm control)	2204	308 (14)	68 (62-72) vs 67 (62-72)
Parkash et al.[57]	2022	RAFT-AF	Catheter ablation vs rate control	411	NR	66 ± 9 68 ± 9
Sohns et al.[24]	2023	CASTLE-HTx	Catheter ablation vs medical therapy	194	NR	62 ± 12 65 ± 10

NR, not reported; PVI, pulmonary vein isolation.
*Patients aged ≥ 75 years receiving ablation in the EAST-AFNET 4 trial.

Table 2. Overview of recent studies on efficacy of catheter ablation in elderly patients

Study and AF phenotype	Patients, young/elderly	Definition of elderly	Design	Follow-up (range) or ± SD	Outcomes
Abdin et al., 2019[51] Mixed AF phenotype	55/183	≥ 75 y	Retrospective, single-centre	11.8 ± 5.4 mo	No difference in arrhythmia recurrence rate (24% vs 27%)
Abugattas et al., 2017[49] Paroxysmal AF	53/106	≥ 75 y	Retrospective, double-centre	14 ± 4.2 mo	No difference in arrhythmia recurrence rate (19% vs 15%)
Boehmer et al., 2024[16] Paroxysmal and persistent AF	268/268	≥ 75 y	Prospective, single-centre, propensity score matching (1:1)	18 mo (12-36 mo)	Higher arrhythmia recurrence rate in elderly: paroxysmal AF: 20% vs 29%; persistent AF: 26% vs 39%
Bulava et al., 2017[61]	50/259	≥ 80 y	Retrospective database analysis	12 mo (all patients)	Higher arrhythmia recurrence rate in elderly with persistent AF: paroxysmal AF: 15% vs 29% (nonsignificant); persistent AF: 19% vs 41%
Cecchini et al., 2022[54] Mixed AF phenotype	70/70	≥ 80 y	Retrospective, multicentre, propensity score matching (1:1)	23 mo (18-32.5 mo)	No difference in arrhythmia recurrence rate (29% vs 40%)
Heeger et al., 2019 [55] Mixed AF phenotype	104/104	≥ 75 y	Retrospective, multicentre, propensit -score matching (1:1)	Elderly: 1.1 y (0.4-2.0 y); control: 1.2 y (0.6-1.5 y)	No difference in arrhythmia recurrence rate (18% vs 20%)
Metzner et al., 2016[48] Mixed AF phenotype	94 elderly	≥ 75 y	Retrospective, single-centre	37 ± 20 mo	Arrhythmia recurrence rates after single procedure: paroxysmal AF: 54%; persistent AF: 69%
Natale et al., 2021[53] Mixed AF phenotype	221/352	≥ 75 y	Prospective, single-centre, only female elderly	48 mo (all patients)	No difference in arrhythmia recurrence rate (47% vs 51%)
Nielsen et al., 2021[52] Mixed AF phenotype	199/1554	≥ 75 y	Retrospective database analysis	12 mo (all patients)	No difference in arrhythmia recurrence rate (HR 1.01)
Tscholl et al., 2018[50] Mixed AF phenotype	40/40	≥ 75 y	Retrospective, single-centre	12 mo (5-18 mo)	No difference in arrhythmia recurrence rate (25% vs 30%)
Willy et al., 2020[62] Persistent AF	146 elderly	≥ 75 y	Prospective ablation registry	231 ± 399 d	Arrhythmia recurrence rates after single procedure 37%

AF, atrial fibrillation; HR, hazard ratio.

which can be programmed according to the patient's needs, and the overall complication rate is relatively low[18,64] and similar to that of PVI[65] (about 3%-7% for PM implantation[66,67]). Although used particularly in elderly patients, data on efficacy and safety of PACE strategy in this specific patient population are almost nonexistent.[21] In a long-term follow-up of the AIRCRAFT study (Australian Intervention Randomised Control of Rate in Atrial Fibrillation Trial), which compared medical rate control with PACE strategy in patients with permanent AF (mean age at time of follow-up ∼ 75 years), both groups showed a reduction in left ventricular ejection fraction (LVEF) of 3% after 5 years (medical 62% vs 59%, PACE 54% vs 51%), with significantly better quality of life in patients with PACE strategy.[20,68]

AVN ablation plus right ventricular (RV) pacing has demonstrated its potential to effectively control heart rate, thereby significantly reducing rehospitalisations and increasing quality of life.[18-20] Results of a large propensity score–matched observational trial demonstrated a 53% reduction in all-cause mortality in patients with a PACE strategy compared with pharmacologic rate control alone.[69] Data for 4444 patients (95%) who had undergone PVI and 234 patients (5%) with AVN ablation from the German Ablation Registry demonstrated similar symptomatic improvement despite older age (4% vs 33% ≥ 75 years) and more cardiovascular comorbidities in those undergoing AVN ablation.[21]

One disadvantage of RV pacing is the induction of left ventricular (LV) dyssynchrony occurring in up to 50% of patients treated with PACE strategy.[70,71] LV dyssynchrony is the strongest predictor of PM-induced cardiomyopathy, which can be detected in about 12% of patients with complete heart block and initially normal LVEF.[71-73] Mittal et al. have shown that in the total of about 11% annual rehospitalisations in patients with univentricular pacing and AVN ablation, almost 90% were due to heart failure (9.4 rehospitalisations per 100 patient-years for heart failure and 1.3 per 100 patient-years for AF).[74] However, PM-induced cardiomyopathy has a response rate of > 80% if an upgrade to cardiac resynchronisation therapy PM can be performed.[73]

Data for first-line therapy using biventricular pacing or conduction system after AVN ablation in patients with LVEF ≥ 50% are very limited,[75] and a clear clinical benefit of physiologic pacing in these patients has not yet been demonstrated.

In this context, patients with LVEF > 45% who undergo AVN ablation and receive biventricular pacing show no improvement in quality of life or in functional capacity (6-minute walk distance) compared with RV pacing.[76] Furthermore, in patients with preserved LV function (without AVN ablation), no improvement in mortality was observed with biventricular[77] or conduction system pacing[78] compared with RV pacing.

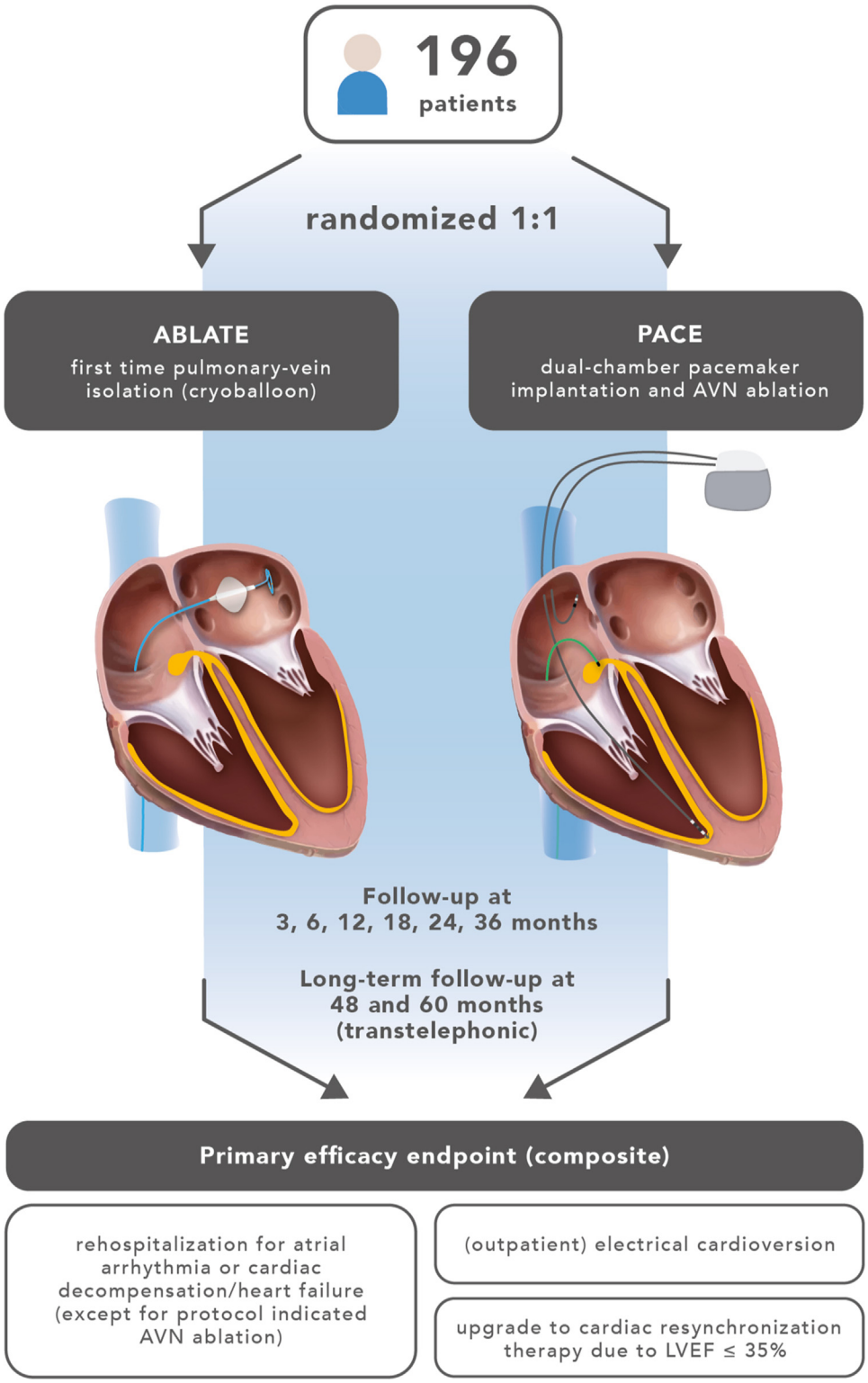

Figure 1. Schematic illustration of ABLATE Versus PACE design and primary efficacy end points. AVN, atrioventricular node; LVEF, left ventricular ejection fraction.

Because the benefit of physiological pacing is low and the risk of procedural complications is estimated to be more than twice as high (8.9% vs 4.1%),[75,79] RV pacing is currently recommended by the ESC,[80] ACC/AHA/ACCP/HRS,[8] and CCS[11] in patients with preserved LVEF undergoing AVN ablation.

Because the primary objective of elderly patients is to avoid hospitalisation, to be free of symptoms and to maximise

Table 3. Inclusion and exclusion criteria of ABLATE Versus PACE trial

Inclusion criteria	• Persistent AF according to current ESC (2020), ACC/AHA/ACCP/HRS (2023), and CCS (2020) guidelines • Symptoms (EHRA functional classification II-IV) despite guideline-indicated medical therapy • Age $\geq$ 75 years • Capability of giving written informed consent
Exclusion criteria	• Previously performed ablation of AF • Impaired systolic left ventricular function (ejection fraction $<$ 50%) • High degree (III°) left cardiac valvular disease • Preimplanted pacemaker • Bradycardia indication for pacemaker • Surgical coronary revascularisation (within the last 90 days) or current triple therapy after percutaneous coronary intervention • Contraindication for pulmonary vein isolation or pacemaker implantation • Contraindication for oral anticoagulation • Body mass index $>$ 40 kg/m^2 • Inability to give written informed consent • Concomitant participation in another registered trial • Reversible cause of AF (eg, thyrotoxicosis, infection, alcohol ingestion) • Life expectancy $<$ 12 months

ACC, American College of Cardiology; ACCP, American College of Chest Physicians; AF, atrial fibrillation; AHA, American Heart Association; CCS, Canadian Cardiovascular Society; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society.

quality instead of quantity of life,[45,46] dual-chamber PM implantation followed by AVN ablation may represent a reasonable alternative particularly for elderly patients.

In the ABLATE Versus PACE trial, patients randomised to PACE will undergo guideline-indicated conventional dual-chamber pacemaker implantation[10,80] followed by AVN ablation. For this trial, cryoenergy was chosen for PVI, because cryoballoon ablation may offer some theoretical advantages over radiofrequency ablation that could be relevant to elderly patients (less new arrhythmogenic tissue and thus reduction in the occurrence of left atrial tachycardia,[31,81] fewer repeated ablation procedures and cardiovascular rehospitalisations,[82] lower incidence of postprocedural left atrial thrombi[83] and silent cerebral infarction,[47,84] and ablation of a relevant part of the pulmonary vein antrum and posterior wall when using a 28-mm balloon[85]).

Methods and Analysis

Study design

ABLATE Versus PACE is an investigator-initiated prospective, open-label, multicentre, randomised superiority trial with blinded end point adjudication (prospective randomised observation with blinded end point evaluation [PROBE] design). A total of 196 patients $\geq$ 75 years of age with symptomatic persistent AF and normal LVEF will be randomised in a 1:1 fashion to cryoballoon PVI or dual-chamber PM implantation and AVN ablation (Fig. 1), designed to achieve a power of 80% with a 2-tailed alpha of 5% for the primary end point (see detailed power calculation below).

Participants

Patients $\geq$ 75 years of age with LVEF $\geq$ 50% and symptomatic persistent AF despite guideline-indicated medical therapy (oral anticoagulation with rhythm or rate control drugs) meeting the inclusion criteria are considered to be candidates for participation in this trial. Table 3 presents the inclusion and exclusion criteria. A screening log regarding inclusion failures will be kept at each site. The ABLATE Versus PACE study is going to include 196 patients (98 for each treatment arm). Written informed consent will be obtained from each study participant before any protocol-specific procedure and after sufficient clarification by either the local principal investigator or one of his or her local representatives.

Screening and randomisation

Eligible patients consenting to participate in the study will be randomised to either the ABLATE (cryoballoon PVI) or the PACE (dual-chamber PM implantation followed by AVN ablation) group. Patients enrolled in the study will be randomised in the order they qualify. Allocation to treatment is based on a predefined randomisation list.

Study setting and timeline

As of July 15, 2024, 10 sites in Germany and Austria have been activated and enrolled 138 patients. We aim to complete enrollment within 12 months (by June 2025). Minimum follow-up will be 12 months.

Study flow

The study flow chart is provided in Table 4. All patients will be followed up for occurrence of primary and secondary end points, performance of echocardiography, and pacemaker interrogation at 3, 6, 12, 18, 24, and 36 months, with a minimum follow-up of 12 months. Quality of life will be assessed with the use of the Atrial Fibrillation Effect on Quality of Life questionnaire (AFEQT). To draw long-term conclusions, patients will be contacted by telephone at 48 and 60 months by the recruiting trial sites, to assess primary efficacy and safety end points.

Interventions are required to be performed within a period of 30 days after randomisation. End points will be counted after PVI or PM insertion/AVN ablation on an intention-to-treat basis. Patients not receiving an intervention will be counted as protocol violations but followed according to protocol.

If patients are unable to visit the study site for follow-up visits, follow-up by telephone is possible as an exception. Further diagnostic evaluation shall be performed at the discretion of the site investigator at the earliest convenience.

Primary efficacy end point

The primary efficacy end point is a combined end point of rehospitalisation for atrial arrhythmia or cardiac decompensation/heart failure, (outpatient) cardioversion, and cardiac resynchronisation therapy PM upgrade due to systolic LVEF reduced to $\leq$ 35% (Fig. 1). Analysis will be performed on an intention-to-treat basis, and patients will be considered enrolled and eligible for analysis at the time of randomisation. In all cases of end point uncertainty, the decision will

Table 4. Study Flow of ABLATE Versuss PACE trial

	Enrollment and intervention			AVN ablation*	Follow-Up							
	Screening	Randomisation	PVI or PM implantation (max 30 d after randomisation)	30 ± 14 d	3 mo ± 14 d	6 mo ± 14 d	12 mo ± 30 d	18 mo ± 30 d	24 mo ± 60 d	36 mo ± 60 d	48 mo ± 90 d (telephone)	60 mo ± 90 d (telephone)
Informed consent	X											
In-/exclusion criteria	X											
Medical history	X				X	X	X	X	X	X	X	X
Concomitant medication	X				X	X	X	X	X	X	X	X
12-lead ECG	X			X	X	X	X	X	X	X		
AFEQT		X			X		X		X	X		
Standard laboratory tests	X											
Echocardiography	X				X	X	X	X	X	X		
Randomisation		X										
PVI/PM implantation			X									
AVN ablation				X								
PM interrogation				X	X	X	X	X	X	X		
Evaluation of clinical events (AEs and SAEs)					X	X	X	X	X	X	X	X

AE, adverse event; AFEQT, Atrial Fibrillation Effect on Quality of Life questionnaire; AVN, atrioventricular node; ECG, electrocardiography; PM, pacemaker; PVI, pulmonary vein isolation; SAE, serious adverse event.

*Only in patients randomised to the PACE group.

Table 5. Primary and secondary end points of the ABLATE Versuss PACE trial

Primary end point (composite)	• Any hospitalisation due to AF, atrial flutter, or atrial tachycardia (except for protocol-indicated AVN ablation), cardiac decompensation/ heart failure with an overnight stay in hospital • (Outpatient) electrical cardioversion for symptomatic relapse of AF, atrial flutter, or atrial tachycardia • Upgrade to CRT pacemaker due to reduced systolic left ventricular function with ejection fraction $\leq$ 35%
Secondary end points	• Death from any cause • Nonfatal or fatal stroke/transient ischemic attack • Any hospitalisation due to AF, atrial flutter or atrial tachycardia or cardiac decompensation/heart failure with an overnight stay in hospital, repeat ablation, or electrical cardioversion for symptomatic relapse of atrial fibrillation, atrial flutter or atrial tachycardia 90 days after index procedure • Procedure-associated complications (major bleeding according to BARC $\geq$ 2 criteria, pacemaker pocket bleeding prolonging inpatient stay, pericardial effusion, cerebrovascular or systemic embolism, phrenic nerve palsy, lead dislodgment, lead perforation, infection including pacemaker pocket infection, lead infection/pacemaker-related endocarditis) • Quality of life assessed by AFEQT • Echocardiographically assessed changes in structural cardiac properties • Prescription of antiarrhythmic drugs after index procedure • Nights spent in hospital due to occurrence of primary end points or procedure-associated complications • Costs to the health care system associated with the treatment of atrial fibrillation (mapped to country-specific diagnosis-related groups) • AF burden and AF progression in patients with implanted devices

AF, atrial fibrillation; AFEQT, Atrial Fibrillation Effect on Quality of Life questionnaire; AVN, atrioventricular node; BARC, Bleeding Academic Research Consortium; CRT, cardiac resynchronisation therapy; ESC, European Society of Cardiology.

be made by the End Point Adjudication Committee composed of 3 cardiologists with expertise in clinical event adjudication.

Secondary end points

Secondary end points focus on procedure-related aspects such as periprocedural complications influencing in-hospital treatment and short-term outcome as well as quality of life and economic implications of either ABLATE or PACE therapy for health care systems. Furthermore, death from any cause, death from stroke or transient ischemic attack, and echocardiographically assessed structural cardiac properties as well as information on antiarrhythmic drug prescriptions or nights spent in hospital for occurrence of primary end points or procedure-related complications are collected for further analysis of patient outcomes. In addition, in patients with implanted devices (PACE arm), AF burden and AF progression to permanent AF will be analysed. A detailed list of prespecified end points is presented in Table 5.

Statistical analysis

The primary efficacy and safety end point analysis will be performed with the use of a Cox regression model with group as a fixed factor and centre as a random variable aiming to superiority of PM implantation and AVN ablation (PACE) vs PVI (ABLATE). The model will be checked by means of Schoenfeld residuals. Because the primary end point is composite, the components will also be analysed separately in a secondary analysis to detect possible imbalances among the components. Multiple events per patient are possible. Repeated events will be analysed within an Andersen and Gill model. In addition, a sensitivity analysis for recurring primary end point events will be performed. Therefore, the number of events will be analysed by calculating $(x + 1)/(y + 1)$ for each patient, where x is the number of the events experienced and y is the number of months in the study. The groups will then be compared by means of a Wilcoxon rank sum test. The number 1 is added in the nominator and the denominator to avoid ties in case of 0 events. Also, the event rate per 100 patient-years will be calculated. Analysis will be performed on an intention-to-treat basis. The significance level is set to $\alpha = 5\%$ (2 sided). The primary analysis population is the intention-to-treat population consisting of all patients randomised to a treatment group.

The AFEQT score will be analysed by an analysis of covariance (ANCOVA) with group as a fixed factor and centre and baseline AFEQT as random variables. Event data (LV function deterioration) will be analysed by a logistic regression model with group as a fixed factor and centre as a random variable.

Because the primary end point is morbidity and not mortality associated, no interim analysis by a data safety monitoring board with potential interruption of the study is planned.

Sample size determination

A fixed sample size design was chosen. For the ABLATE group, we anticipate a 1-year arrhythmia/rehospitalisation rate of 25%-40% based on previous studies.[14,31,33,42] Fewer data are available for the PACE group, with reported annual rehospitalisation rates of around 11%.[74] Given these data, we assume a 1-year event rate of primary end points of 35% (ABLATE) and 15% (PACE). For a power of 80% with an alpha of 5% (2 sided), this results in a required case load of 73 patients per group. With an anticipated dropout rate of 10%, expected crossover rate of 5% ,and a safety margin of 10%, this results in a case load of 98 patients per group ($\sim$73/[1 $-$

0.25]). The sample size was calculated with SAS version 9.4 using a log rank test.

Study coordination, committees, and end point adjudication

St Josefs-Hospital, Wiesbaden, Germany, will coordinate the study. The centre will specifically be responsible for the randomisation process and for receiving, editing, processing, analysing, and storing data generated in this trial.

All end points will be adjudicated by the blinded End Point Adjudication Committee. This committee will consist of 3 electrophysiologists not directly involved in the study with expertise in clinical event adjudication. The End Point Adjudication Committee members are independent and have no conflict of interest with the present study or its investigators. As soon as the study is completed, the results will be presented at international conferences with concomitant publication in an indexed journal.

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Summary and Conclusion

Elderly patients are at high risk of developing AF.[86-89] Although PVI is the most effective means of rhythm control and may be considered as first-line therapy for rhythm control in patients with persistent AF (ESC guidelines: class IIb recommendation[9]; ACC/AHA/ACCP/HRS guidelines: class IIa recommendation[10]), the efficacy of PVI decreases with age and duration of AF.[17,60,61,90] Some physicians may extrapolate these recommendations to a much larger population base than that for which persuasive data exist, in particular the large group of elderly individuals ($\geq$ 75 years of age).

In fact, there are only sparse prospective data on the efficacy and safety of PVI in elderly patients. Studies addressing this population are mostly observational and nonrandomised and indicate limited efficacy.[16,17,48,60,61] These patients are consequently subject to recurrent arrhythmia-related procedures and hospitalisations with an increased risk of procedure- and hospital-associated complications.[91] Because AVN ablation with ventricular pacing may reduce arrhythmia related therapy by providing a permanent solution,[45,46] a rate control (PACE) strategy may provide better symptom control and quality of life than a rhythm control (ABLATE) strategy.

This study will test whether a PACE strategy—compared with an ABLATE strategy—will significantly reduce rehospitalisations and interventions due to recurrence of atrial arrhythmia or heart failure and thereby improve quality of life in patients $\geq$ 75 years of age with symptomatic persistent AF and normal LVEF.

The results of the ABLATE Versus PACE trial will support evidence-based decision making for the optimal treatment of elderly patients with persistent symptomatic AF and normal LVEF.

Ethics Statement

The ABLATE versus PACE trial has been approved by the coordinating ethics committee (Landesärztekammer Hessen, Germany) as well as by all regional ethics committees responsible for the local study sites.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a study design paper. Therefore, patient consent is not required.

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Disclosures

The authors have no conflicts of interest to disclose.

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References

1. de Vos CB, Pisters R, Nieuwlaat R, et al. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. J Am Coll Cardiol 2010;55:725-31.
2. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J 2013;34:2746-51.
3. Timmis A, Vardas P, Townsend N, et al. European Society of Cardiology: cardiovascular disease statistics 2021. Eur Heart J 2022;43:716-99.
4. Pallisgaard JL, Gislason GH, Hansen J, et al. Temporal trends in atrial fibrillation recurrence rates after ablation between 2005 and 2014: a nationwide Danish cohort study. Eur Heart J 2018;39:442-9.
5. Holmqvist F, Kesek M, Englund A, et al. A decade of catheter ablation of cardiac arrhythmias in Sweden: ablation practices and outcomes. Eur Heart J 2019;40:820-30.
6. Eckardt L, Doldi F, Busch S, et al. 10-year follow-up of interventional electrophysiology: updated German survey during the Covid-19 pandemic. Clin Res Cardiol 2023;112:784-94.
7. Willems S, Meyer C, de Bono J, et al. Cabins, castles, and constant hearts: rhythm control therapy in patients with atrial fibrillation. Eur Heart J 2019;40:3793-3799c.
8. Wasmer K, Eckardt L, Breithardt G. Predisposing factors for atrial fibrillation in the elderly. J Geriatr Cardiol 2017;14:179-84.
9. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42:373-498.

10. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2024;149:e1-156.

11. Andrade JG, Aguilar M, Atzema C, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society comprehensive guidelines for the management of atrial fibrillation. Can J Cardiol 2020;36:1847-948.

12. Kirchhof P, Camm AJ, Goette A, et al. Early rhythm-control therapy in patients with atrial fibrillation. N Engl J Med 2020;383:1305-16.

13. Schnabel RB, Marinelli EA, Arbelo E, et al. Early diagnosis and better rhythm management to improve outcomes in patients with atrial fibrillation: the 8th AFNET/EHRA consensus conference. Europace 2023;25:6-27.

14. Andrade JG, Wells GA, Deyell MW, et al. Cryoablation or drug therapy for initial treatment of atrial fibrillation. N Engl J Med 2021;384:305-15.

15. Wazni OM, Dandamudi G, Sood N, et al. Cryoballoon ablation as initial therapy for atrial fibrillation. N Engl J Med 2021;384:316-24.

16. Boehmer AA, Rothe M, Keim C, et al. Pulmonary vein isolation in elderly patients ≥ 75 years: a propensity-score matched analysis with focus on differences between atrial fibrillation types. Can J Cardiol 2024;40:1541-50.

17. Vermeersch G, Abugattas JP, Varnavas V, et al. Efficacy and safety of the second-generation cryoballoon ablation for the treatment of persistent atrial fibrillation in elderly patients. J Arrhythm 2021;37:626-34.

18. Jensen SM, Bergfeldt L, Rosenqvist M. Long-term follow-up of patients treated by radiofrequency ablation of the atrioventricular junction. Pacing Clin Electrophysiol 1995;18(9 Pt 1):1609-14.

19. Chatterjee NA, Upadhyay GA, Ellenbogen KA, et al. Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis and systematic review. Circ Arrhythm Electrophysiol 2012;5:68-76.

20. Weerasooriya R, Davis M, Powell A, et al. The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT). J Am Coll Cardiol 2003;41:1697-702.

21. Wasmer K, Hochadel M, Wieneke H, et al. Long-term symptom improvement and patient satisfaction after AV-node ablation vs pulmonary vein isolation for symptomatic atrial fibrillation: results from the German Ablation Registry. Clin Res Cardiol 2019;108:395-401.

22. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378:417-27.

23. Di Biase L, Mohanty P, Mohanty S, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. Circulation 2016;133:1637-44.

24. Sohns C, Fox H, Marrouche NF, et al. Catheter ablation in end-stage heart failure with atrial fibrillation. N Engl J Med 2023;389:1380-9.

25. Eckardt L, Wolfes J, Frommeyer G. Benefits of early rhythm control of atrial fibrillation. Trends Cardiovasc Med 2024;34:288-94.

26. Andrade JG, Deyell MW, Khairy P, et al. Atrial fibrillation progression after cryoablation versus radiofrequency ablation: the CIRCA-DOSE trial. Eur Heart J 2024;45:510-8.

27. Andrade JG, Deyell MW, Macle L, et al. Progression of atrial fibrillation after cryoablation or drug therapy. N Engl J Med 2023;388:105-16.

28. Packer DL, Piccini JP, Monahan KH, et al. Ablation versus drug therapy for atrial fibrillation in heart failure: results from the CABANA trial. Circulation 2021;143:1377-90.

29. Konemann H, Guler-Eren S, Ellermann C, Frommeyer G, Eckardt L. Antiarrhythmic treatment in heart failure. Curr Heart Fail Rep 2024;21:22-32.

30. Eckardt L, Sehner S, Suling A, et al. Attaining sinus rhythm mediates improved outcome with early rhythm control therapy of atrial fibrillation: the EAST-AFNET 4 trial. Eur Heart J 2022;43:4127-44.

31. Kuck KH, Brugada J, Furnkranz A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med 2016;374:2235-45.

32. Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. J Am Coll Cardiol 2013;61:1713-23.

33. Reddy VY, Gerstenfeld EP, Natale A, et al. Pulsed field or conventional thermal ablation for paroxysmal atrial fibrillation. N Engl J Med 2023;389:1660-71.

34. Mont L, Bisbal F, Hernandez-Madrid A, et al. Catheter ablation vs antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). Eur Heart J 2014;35:501-7.

35. Su WW, Reddy VY, Bhasin K, et al. Cryoballoon ablation of pulmonary veins for persistent atrial fibrillation: results from the multicenter STOP Persistent AF trial. Heart Rhythm 2020;17:1841-7.

36. Moser JM, Willems S, Andresen D, et al. Complication rates of catheter ablation of atrial fibrillation in patients aged ≥75 years versus <75 years—results from the German Ablation Registry. J Cardiovasc Electrophysiol 2017;28:258-65.

37. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015;372:1812-22.

38. Vogler J, Willems S, Sultan A, et al. Pulmonary vein isolation versus defragmentation: the CHASE-AF clinical trial. J Am Coll Cardiol 2015;66:2743-52.

39. Kistler PM, Chieng D, Sugumar H, et al. Effect of catheter ablation using pulmonary vein isolation with vs without posterior left atrial wall isolation on atrial arrhythmia recurrence in patients with persistent atrial fibrillation: the CAPLA randomized clinical trial. JAMA 2023;329:127-35.

40. Gunawardene MA, Frommeyer G, Ellermann C, et al. Left atrial posterior wall isolation with pulsed field ablation in persistent atrial fibrillation. J Clin Med 2023;12:6304.

41. Prabhu S, Taylor AJ, Costello BT, et al. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. J Am Coll Cardiol 2017;70:1949-61.

42. Kuck KH, Furnkranz A, Chun KR, et al. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. Eur Heart J 2016;37:2858-65.

43. Willems S, Khairy P, Andrade JG, et al. Redefining the blanking period after catheter ablation for paroxysmal atrial fibrillation: insights from the ADVICE (Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination) trial. Circ Arrhythm Electrophysiol 2016;9:e003909.

44. Noujaim C, Lim C, Mekhael M, et al. Identifying the prognostic significance of early arrhythmia recurrence during the blanking period and

the optimal blanking period duration: insights from the DECAAF II study. Europace 2023;25:euad173.

45. Waller A, Sanson-Fisher R, Nair BR, Evans T. Preferences for end-of-life care and decision making among older and seriously ill inpatients: a cross-sectional study. J Pain Symptom Manage 2020;59:187-96.

46. Olsson IN, Runnamo R, Engfeldt P. Medication quality and quality of life in the elderly, a cohort study. Health Qual Life Outcomes 2011;9:95.

47. Gaita F, Leclercq JF, Schumacher B, et al. Incidence of silent cerebral thromboembolic lesions after atrial fibrillation ablation may change according to technology used: comparison of irrigated radiofrequency, multipolar nonirrigated catheter and cryoballoon. J Cardiovasc Electrophysiol 2011;22:961-8.

48. Metzner I, Wissner E, Tilz RR, et al. Ablation of atrial fibrillation in patients ≥75 years: long-term clinical outcome and safety. Europace 2016;18:543-9.

49. Abugattas JP, Iacopino S, Moran D, et al. Efficacy and safety of the second generation cryoballoon ablation for the treatment of paroxysmal atrial fibrillation in patients over 75 years: a comparison with a younger cohort. Europace 2017;19:1798-803.

50. Tscholl V, Lin T, Lsharaf AK, et al. Cryoballoon ablation in the elderly: one year outcome and safety of the second-generation 28mm cryoballoon in patients over 75 years old. Europace 2018;20:772-7.

51. Abdin A, Yalin K, Lyan E, et al. Safety and efficacy of cryoballoon ablation for the treatment of atrial fibrillation in elderly patients. Clin Res Cardiol 2019;108:167-74.

52. Nielsen J, Kragholm KH, Christensen SB, et al. Periprocedural complications and one-year outcomes after catheter ablation for treatment of atrial fibrillation in elderly patients: a nationwide Danish cohort study. J Geriatr Cardiol 2021;18:897-907.

53. Natale V, Mohanty S, Trivedi C, et al. Arrhythmia profile and ablation-outcome in elderly women with atrial fibrillation undergoing first catheter ablation. Pacing Clin Electrophysiol 2021;44:835-42.

54. Cecchini F, Mugnai G, Iacopino S, et al. Safety and long-term efficacy of cryoballoon ablation for atrial fibrillation in octogenarians: a multicenter experience. J Interv Card Electrophysiol 2022;65:559-71.

55. Heeger CH, Bellmann B, Fink T, et al. Efficacy and safety of cryoballoon ablation in the elderly: a multicenter study. Int J Cardiol 2019;278:108-13.

56. Boveda S, Metzner A, Nguyen DQ, et al. Single-procedure outcomes and quality-of-life improvement 12 months post—cryoballoon ablation in persistent atrial fibrillation: results from the multicenter CRYO4PERSISTENT AF trial. JACC Clin Electrophysiol 2018;4:1440-7.

57. Parkash R, Wells GA, Rouleau J, et al. Randomized ablation-based rhythm-control versus rate-control trial in patients with heart failure and atrial fibrillation: results from the RAFT-AF trial. Circulation 2022;145:1693-704.

58. Kim D, Yang PS, You SC, et al. Age and outcomes of early rhythm control in patients with atrial fibrillation: nationwide cohort study. JACC Clin Electrophysiol 2022;8:619-32.

59. Bahnson TD, Giczewska A, Mark DB, et al. Association between age and outcomes of catheter ablation versus medical therapy for atrial fibrillation: results from the CABANA trial. Circulation 2022;145:796-804.

60. Boehmer AA, Rothe M, Zezyk C, et al. Persistent atrial fibrillation in elderly patients: limited efficacy of pulmonary vein isolation. J Clin Med 2022;11:6070.

61. Bulava A, Hanis J, Dusek L. Clinical outcomes of radiofrequency catheter ablation of atrial fibrillation in octogenarians—10-year experience of a one high-volume center. J Geriatr Cardiol 2017;14:575-81.

62. Willy K, Wasmer K, Dechering DG, et al. Ablation of paroxysmal and persistent atrial fibrillation in the very elderly real-world data on safety and efficacy. Clin Cardiol 2020;43:1579-84.

63. Boehmer AA, Rothe M, Ruckes C, et al. Catheter ablation for atrial fibrillation in elderly patients: an updated meta-analysis of comparative studies. Can J Cardiol 2024;40:2441-51.

64. Vlachos K, Letsas KP, Korantzopoulos P, et al. A review on atrioventricular junction ablation and pacing for heart rate control of atrial fibrillation. J Geriatr Cardiol 2015;12:547-54.

65. Khan MN, Jais P, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. N Engl J Med 2008;359:1778-85.

66. Parsonnet V, Bernstein AD, Lindsay B. Pacemaker-implantation complication rates: an analysis of some contributing factors. J Am Coll Cardiol 1989;13:917-21.

67. Eberhardt F, Bode F, Bonnemeier H, et al. Long term complications in single and dual chamber pacing are influenced by surgical experience and patient morbidity. Heart 2005;91:500-6.

68. Lim KT, Davis MJ, Powell A, et al. Ablate and pace strategy for atrial fibrillation: long-term outcome of AIRCRAFT trial. Europace 2007;9:498-505.

69. Garcia B, Clementy N, Benhenda N, et al. Mortality after atrioventricular nodal radiofrequency catheter ablation with permanent ventricular pacing in atrial fibrillation: outcomes from a controlled nonrandomized study. Circ Arrhythm Electrophysiol 2016;9:e003993.

70. Tops LF, Schalij MJ, Holman ER, et al. Right ventricular pacing can induce ventricular dyssynchrony in patients with atrial fibrillation after atrioventricular node ablation. J Am Coll Cardiol 2006;48:1642-8.

71. Huizar JF, Kaszala K, Tan A, et al. Abnormal conduction-induced cardiomyopathy: JACC review topic of the week. J Am Coll Cardiol 2023;81:1192-200.

72. Bansal R, Parakh N, Gupta A, et al. Incidence and predictors of pacemaker-induced cardiomyopathy with comparison between apical and nonapical right ventricular pacing sites. J Interv Card Electrophysiol 2019;56:63-70.

73. Kiehl EL, Makki T, Kumar R, et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy in patients with complete atrioventricular block and preserved left ventricular systolic function. Heart Rhythm 2016;13:2272-8.

74. Mittal S, Musat DL, Hoskins MH, et al. Clinical outcomes after ablation of the AV junction in patients with atrial fibrillation: impact of cardiac resynchronization therapy. J Am Heart Assoc 2017;6:e007270.

75. Slotwiner DJ, Raitt MH, Del-Carpio Munoz F, et al. Impact of physiologic pacing versus right ventricular pacing among patients with left ventricular ejection fraction greater than 35%: a systematic review for the 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019;74:988-1008.

76. Doshi RN, Daoud EG, Fellows C, et al. Left ventricular—based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). J Cardiovasc Electrophysiol 2005;16:1160-5.

77. Yu CM, Chan JY, Zhang Q, et al. Biventricular pacing in patients with bradycardia and normal ejection fraction. N Engl J Med 2009;361:2123-34.

78. Kronborg MB, Mortensen PT, Poulsen SH, et al. His or para-His pacing preserves left ventricular function in atrioventricular block: a double-blind, randomized, crossover study. Europace 2014;16:1189-96.

79. Chatterjee NA, Upadhyay GA, Ellenbogen KA, Hayes DL, Singh JP. Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis of biventricular vs right ventricular pacing mode. Eur J Heart Fail 2012;14:661-7.

80. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J 2021;42:3427-520.

81. Kuck KH, Brugada J, Schluter M, et al. The FIRE AND ICE trial: what we know, what we can still learn, and what we need to address in the future. J Am Heart Assoc 2018;7:e010777.

82. Chun KRJ, Brugada J, Elvan A, et al. The impact of cryoballoon versus radiofrequency ablation for paroxysmal atrial fibrillation on healthcare utilization and costs: an economic analysis from the FIRE AND ICE trial. J Am Heart Assoc 2017;6:e006043.

83. Khairy P, Chauvet P, Lehmann J, et al. Lower incidence of thrombus formation with cryoenergy versus radiofrequency catheter ablation. Circulation 2003;107:2045-50.

84. Herrera Siklody C, Deneke T, Hocini M, et al. Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation: comparison of different atrial fibrillation ablation technologies in a multicenter study. J Am Coll Cardiol 2011;58:681-8.

85. Kenigsberg DN, Martin N, Lim HW, Kowalski M, Ellenbogen KA. Quantification of the cryoablation zone demarcated by pre- and post-procedural electroanatomic mapping in patients with atrial fibrillation using the 28-mm second-generation cryoballoon. Heart Rhythm 2015;12:283-90.

86. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med 1982;306:1018-22.

87. Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 2006;27:949-53.

88. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 study. Circulation 2014;129:837-47.

89. Nielsen JC, Lin YJ, de Oliveira Figueiredo MJ, et al; European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS). expert consensus on risk assessment in cardiac arrhythmias: use the right tool for the right outcome, in the right population. Europace 2020;22:1147-8.

90. Chun KR, Schmidt B, Kuck KH, et al. Catheter ablation of atrial fibrillation in the young: insights from the German Ablation Registry. Clin Res Cardiol 2013;102:459-68.

91. Mudge AM, McRae P, Hubbard RE, et al. Hospital-associated complications of older people: a proposed multicomponent outcome for acute care. J Am Geriatr Soc 2019;67:352-6.