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ORIGINAL PAPER

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

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Abstract

Background We aimed to compare patient characteristics and outcome of patients who had either undergone pulmonary vein isolation (PVI) or AV-node ablation (AVN) to control AF-related symptoms.

Methods From the German Ablation Registry, we analyzed data of 4444 patients (95%) who had undergone PVI and 234 patients (5%) with AVN.

Results AVN patients were on average 10 years older than PVI patients (71 ± 10 vs. 61 ± 10 years, $p < 0.001$) with 33% aged > 75 years. AVN patients had significantly more cardiovascular comorbidities (diabetes 21% vs. 8%, renal insufficiency 24% vs. 3%, underlying heart disease 80% vs. 36%, severely reduced left ventricular function 28% vs. 1%, all $p < 0.001$). Significantly more PVI patients had paroxysmal AF (63% vs. 18%, $p < 0.001$), and more AVN patients had long-standing persistent AF (44% vs. 7%, $p < 0.001$). At 1-year follow-up, mortality in the AVN group was much higher (Kaplan–Meier estimates 9.8% vs. 0.5%). 20% of PVI patients had undergone another ablation vs. 3% AVN patients ($p < 0.001$). Symptomatic improvement was equally achieved in about 80%. Re-hospitalization for cardiovascular reasons occurred significantly more often in PVI vs. AVN patients (31% vs. 18%, $p < 0.001$).

Conclusion In the large German Ablation Registry, AVN ablation was performed much less frequently than PVI for symptomatic treatment of AF and typically in older patients with more comorbidity. Symptomatic improvement was similar in both groups. Hospitalizations for cardiovascular reasons were lower in AVN patients despite older age and more cardiovascular comorbidities. 20% of PVI patients had undergone at least one re-ablation.

Keywords Atrial fibrillation · Pulmonary vein isolation · AV-node ablation · Symptomatic improvement

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Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia responsible for significant morbidity and health care costs. Treatment concepts include rate or rhythm control based on symptoms [1–3]. Symptomatic patients receive trials of antiarrhythmic drugs and/or undergo pulmonary vein isolation (PVI) to improve their symptoms. Ablation of the atrioventricular node (AVN) after prior implantation of a pacemaker can control rate and symptoms when medication and catheter ablation fail. Randomized trials that compared rate and rhythm control strategies have included relatively older patients [4–6]. These studies, that were published when PVI just became available, compared rhythm control with antiarrhythmic drugs and did not show inferiority of rate control over rhythm control with respect to death and morbidity from cardiovascular causes including patients with heart failure [7]. Since then different ablation techniques and technologies for PVI have evolved and it has now become one of the most frequently performed ablation procedures [8]. Despite its extensive use and evaluation, a significant proportion of patients remain in AF despite repeat PVI procedures. AVN-ablation is often considered for these patients to improve their debilitating symptoms. This approach is considered "last resort" by many because it renders the patient pacemaker dependent for the rest of his/her life. Therefore, it is more often performed in older patients.

PVI and AVN-ablation have both been evaluated in numerous trials and directly compared in randomized trials [9], but less is known about real-world outcome of both PVI and AVN. The German Ablation Registry was initiated to study patient characteristics and clinical outcome of both treatment strategies in a large real-world multicenter ablation cohort.

Methods

The German Ablation Registry prospectively collected data on cardiac ablation procedures between January 2007 and January 2010. The registry has been described in detail elsewhere [10]. In brief, 52 voluntarily participating German centers included consecutive consented patients. Participating centers reported data in internet-based electronic case report forms. The industry-independent foundation "Stiftung Institut für Herzinfarktforschung" (IHF) in Ludwigshafen has been responsible for project development and management, data management and patient follow-up. The study was approved by the Ethics Committee at the state chamber of physicians Rheinland-Pfalz.

Data collection

Patient characteristics (including age, sex, symptoms, details of cardiac disease, NYHA class in patients with cardiac disease, and comorbidities), ablation methods, procedural parameters and outcome, acute complications and drugs at discharge were documented at baseline. Patients were treated according to the ablation standards of the ablation centers. The indication for the procedure as well as the choice of ablation technology and ablation strategy was left to the preference of the individual ablation center. After at least 1 year of enrolment, patients were contacted by phone and interrogated about complications, recurrences, new ablations, and symptoms.

Statistical analysis

Continuous data are reported as median (interquartile range) or mean ± SD, and categorical data are reported as percentages. Determinants for the use of AV-node ablations were analyzed by multiple logistic regression, including the significantly different ($p < 0.001$) and clinically important patient characteristics as potential explanatory variables. The model results are presented as odds ratios with 95% confidence intervals and discrimination was assessed with the *C* statistic.

Follow-up duration was defined as the interval between date of discharge and date of follow-up contact. One-year mortality was estimated by means of survival analysis. For relevant follow-up events, rates with 95% confidence intervals are shown that were calculated by the Pearson–Clopper method for binary variables and the delta method with log-transformation for Kaplan–Meier estimates. Regarding the extreme selection of the AVN patients, no attempt to evaluate adjusted effects was made. p values ≤ 0.05 were considered significant without allowance for multiple testing. All p values are results of two-tailed tests. The statistical computations were performed using SAS release 9.3 on a personal computer (SAS Institute, Inc., Cary, NC, USA).

Results

Between 2007 and 2010, 4678 patients with symptomatic AF who underwent either a pulmonary vein isolation procedure ($n = 4444$) or AVN-ablation ($n = 234$) were included in the registry.

Patient characteristics

Clinical characteristics are summarized in Table 1. The vast majority of patients had undergone PVI (ratio 19:1).

Table 1 Patient characteristics

	AVN-ablation	PVI	*p* value
No. of patients	234	4444	
Men	132 (56.4%)	3201 (68.0%)	< 0.001
Age	71 ± 10	61 ± 10	< 0.001
Age > 75 years	33%	3.8%	< 0.001
Paroxysmal AF	18%	63%	< 0.001
Persistent AF	38%	30%	0.006
Long-standing persistent AF	44%	7%	< 0.001
Hypertension	70%	62%	0.30
Diabetes	21%	8%	< 0.001
Coronary artery disease	42%	18%	< 0.001
Previous MI	12%	5%	< 0.001
Cardiomyopathy	24%	4%	< 0.001
DCM	96.4%	71.8%	
HCM	3.6%	28.2%	
Hypertensive CM	22%	12%	< 0.001
Normal LV function	36%	86%	< 0.001
Reduced LV function < 30%	28%	1%	< 0.001
NYHA ≥ II[a]	82%	42%	< 0.001

No. number, *AF* atrial fibrillation, *MI* myocardial infarction, *CM* cardiomyopathy, *DCM* dilated cardiomyopathy, *HCM* hypertrophic cardiomyopathy, *LV* left ventricle, *NYHA* New York Heart Association class of heart failure

[a]NYHA class was only obtained in patients with structural heart disease

Patients with AVN-ablation were significantly older, one-third was older than 75 years, and the proportion of women was significantly higher. They had significantly more often structural heart disease, left ventricular dysfunction, and cardiovascular comorbidities. Persistent and long-standing persistent AFs were the predominant AF types in patients with AV-node ablation compared to paroxysmal and persistent AF in patients who underwent PVI.

Procedural characteristics and acute outcome

Procedural parameters, acute success, and procedure-related complications are summarized in Table 2. The majority of PVI procedures were performed with radiofrequency energy (81.5%), and less frequently with cryo-energy. Sole PVI was reported in 76% of cases, additional linear lesions in 17% and ablation of fractionated potentials in 12%. Nine percent of patients with AVN-ablation as the index procedure had undergone a previous ablation compared to 18% of patients with PVI. Procedural time and fluoroscopy time were shorter for AVN-ablation procedures compared to PVI. Acute procedural success was not different and almost 100% for both ablation types.

Table 2 Procedural parameters and acute outcome

	AVN-ablation	PVI	*p* value
Single ablation procedure	98%	98%	0.8*
First ablation	91%	82%	< 0.001*
Acute procedural success	97%	96%	0.47*
Fluoroscopy time (min)	13 ± 15	35 ± 24	< 0.001
Procedure duration (min)	67 ± 55	179 ± 71	< 0.001
Major complications	0%	1.1%	0.17*
Moderate complications	2.9%	3.1%	1.00*
Minor complications	0.5%	3.5%	0.015*
Duration of stay (days)	5 (2–12)	3 (2–5)	< 0.001
Discharge on			
Beta-blocker	65.5%	73.4%	0.008
Digitalis	24.6%	4.1%	< 0.001
Discharge off AD	83.6%	46.0%	< 0.001
Discharge on VKA	79.2%	90.3%	< 0.001

Min minutes, *AD* antiarrhythmic drugs class I and III, *VKA* vitamin K antagonist

*p value calculated by Fisher's exact test

There were only minor differences regarding in-hospital complications. No non-fatal major complications occurred in the AVN ablation group, but in 1.1% of PVI patients [stroke in 0.2% and major bleeding in 0.8%, cardiac surgery in three patients (0.1%)]. Pericardial effusion was reported in 0.5% in the AVN-ablation group compared to 1.1% in the PVI group, minor bleeding (not requiring intervention) in 0.5% compared to 3% in the PVI group. One pneumothorax occurred in the AVN-ablation group, while 15 patients in the PVI group had phrenic nerve palsy and three patients had pulmonary vein stenosis.

One patient in the AVN-ablation group with severe cardiomyopathy died suddenly during hospital stay, and one patient with PVI following unsuccessful cardiac resuscitation. He was reported to have had complete heart block and pericardial effusion, but no detailed information on the circumstances of his death is known.

At discharge, 66% of AVN-ablation patients were using beta-blockers compared to 73% in the PVI group. Significantly more patients in the PVI group (54%) compared to patients in the AVN-ablation group (16%) was on antiarrhythmic drugs at discharge. Consistent with their comorbidities, more patients in the AVN-ablation group were taking diuretics, statins, ACE-inhibitors, and/or angiotensin blockers (each $p < 0.001$). Seventy-nine percent of patients in the AVN-ablation group and 90% of patients in the PVI group were using oral anticoagulation at the time of discharge ($p < 0.001$).

A multivariable analysis of determinants revealed that the clinically relevant patient characteristics listed in Table 3 are not only differently distributed between treatment groups but

Table 3 Determinants of indication for AVN ablation

	Unifactorial OR (95% CI)	MV-OR (95% CI)	*p* value
Age (per 10 year increase)	3.91 (3.23–4.73)	3.60 (2.83–4.58)	< 0.001
Female gender	1.64 (1.26–2.14)	1.91 (1.33–2.74)	< 0.001
Persistent vs. paroxysmal AF	4.61 (3.17–6.72)	3.14 (2.06–4.78)	< 0.001
Long-standing persistent vs. paroxysmal AF	22.10 (15.11–32.31)	12.39 (7.86–19.54)	< 0.001
Diabetes	3.28 (2.35–4.57)	1.67 (1.05–2.64)	0.029
Coronary artery disease	3.25 (2.48–4.27)	1.56 (1.07–2.29)	0.022
Cardiomyopathy	8.65 (6.15–12.15)	2.50 (1.36–4.59)	0.003
LVEF ≤ 40%	19.76 (14.58–26.78)	5.24 (3.21–8.56)	< 0.001
NYHA class > II	42.33 (29.64–60.45)	7.49 (4.44–12.64)	< 0.001

$C = 0.919$

LVEF left ventricular ejection fraction, *NYHA* New York Heart Association classification for heart failure, *OR* Odds ratio, *MV* multivariable, *CI* confidence interval

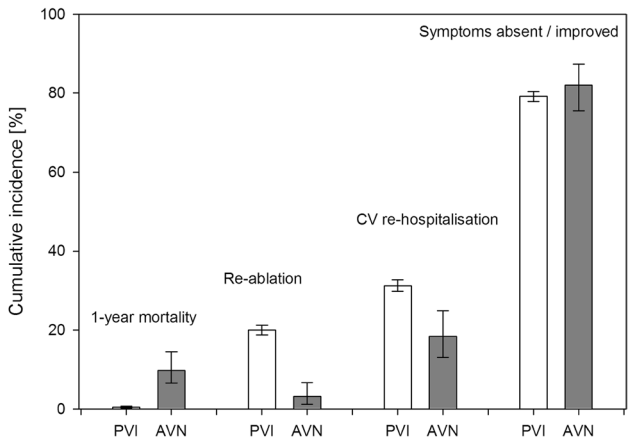

Fig. 1 Follow-up outcome data

contribute independently to the indication for AVN ablation. The very high *C* statistic of 0.919 indicates that the decision to use AVN ablation is determined to a large extent by these criteria. Heart failure > NYHA II, non-paroxysmal AF, reduced EF and age were the strongest determinants in univariate analysis. On multivariate analysis, these parameters remained the strongest determinants.

Follow-up results

Follow-up data were obtained in 97% of AVN-ablation patients at a median of 456 days after index discharge (IQR 397–533) and 98% of PVI patients at a median of 460 days (IQR 407–534) (p = n.s.). Follow-up outcome data are displayed in Fig. 1. One-year mortality was significantly higher in the AVN-ablation group (9.8%) compared to the PVI group (0.5%; $p < 0.001$). However, the causes of death were distributed similarly, with 10% vs. 7% reported non-cardiac causes. More major adverse events had occurred in the AVN-ablation group compared to the PVI group (3.8% vs. 1.8%, $p = 0.048$), predominantly major bleeding events (2.8% vs. 1.0%, $p = 0.046$) and stroke (1.7% vs. 0.5%, $p = 0.086$). Procedure related complications were reported in 0.6% of PVI patients, PV stenosis in 0.1% and phrenic nerve palsy in 0.5%. No procedure associated complications were reported in the AVN-ablation group.

A re-ablation during 1 year after the index procedure was performed in 3.1% of the AVN-ablation group and 20.0% of the PVI group ($p < 0.001$). A mean of 1.6 re-hospitalizations were reported in both groups, occurring in 37% and 39% of patients. While patients in the PVI group were hospitalized for cardiovascular reasons in 79% of cases, more than half of patients in the AVN-ablation group (51%) were hospitalized for non-cardiac reasons ($p < 0.001$). Their hospital stay was also significantly longer (19 ± 23 days) compared to PVI patients (10 ± 13 days, $p < 0.001$).

Symptom improvement was reported by 65% of AVN-ablation patients and 62% of PVI patients ($p = 0.4$), absence of symptoms by 17% in both groups ($p = 0.9$). Unchanged symptoms were reported by 15% and 18% ($p = 0.4$), respectively, and worsened symptoms by 3% in both groups ($p = 0.73$). The proportion of asymptomatic patients was not different between groups (16.6% and 17.1%, $p = 0.92$).

Discussion

Our analysis of data from a large prospective ablation registry, representing 52 ablation centers in Germany, reveals that symptomatic improvement was equally achieved by means of PVI and AVN-ablation in approximately two-thirds of patients.

PVI is the leading ablation strategy for patients with symptomatic AF. 95% of patients in this prospective registry underwent PVI compared to 5% who underwent

AVN-ablation. Apparently, AVN-ablation is considered as last resort and performed predominantly in older patients with more comorbidities. Mean age in patients with AVN-ablation was 71 years, 10 years older than PVI patients. The mean age of 71 years is almost identical to the mean age of patients in the large randomized trials comparing rate vs. rhythm control [4]. One-third of patients with AVN-ablation were > 75 years old. In addition, significantly more patients with AVN-ablation had underlying structural heart disease, LV dysfunction, and comorbidities such as hypertension or diabetes. These risk factors are also known to be associated with lower success of PVI [1]. This is also true for more progressed forms of AF like persistent and long-standing persistent AF. The proportion of patients with paroxysmal AF was, therefore, much higher in PVI patients compared to patients who had undergone AVN-ablation. Although detailed information regarding clinical decision making, i.e., the indication for AVN ablation vs. PVI in a given patient, was not documented in this registry, therapeutic decisions regarding patients with symptomatic AF in this registry appear to mirror current guideline recommendations that have continuously increased the indications for PVI [1–3]. In contrast, current guidelines mention AVN-ablation as a possible intervention to control heart rate and symptoms when medication fails. The associated life-long pacemaker dependency is rated as a significant limitation. According to current guidelines, AVN-ablation is, therefore, considerable if symptoms cannot be managed by rate-controlling medication or reasonable rhythm control interventions [1–3].

Symptom improvement

So far, symptomatic improvement is the indication for any AF treatment strategy, including both PVI and AVN-ablation [1]. Importantly, this was equally achieved with both treatment strategies in approximately 80% of patients. This is also reflected by improvement in NYHA class ≥ II in patients with structural heart disease, decreasing from 82 to 65% in the AVN-ablation group and to a lesser extent from 42 to 34% in PVI patients.

However, the "healthier" patients undergoing PVI to achieve symptomatic improvement had to pay a higher price compared to patients who underwent AVN-ablation, although the overall complication rate was low. Procedure duration and fluoroscopy time were longer with PVI, more minor and major complications were reported in the PVI group, and more frequent re-hospitalizations for cardiovascular reasons were observed in patients with PVI. A higher rate of hospitalizations with rhythm control strategies has been reported previously [11, 12]. The underlying reasons remain unknown from this registry, but it is noteworthy, particularly in the light of older age and higher cardiovascular morbidities in the AVN-ablation patients. Both, age and comorbidities, likely explain the higher mortality at 1 year in the AVN-ablation group. Prognostic influence of PVI may play a role as well, although this question cannot be answered from these registry data.

Despite PVI, only 46% of patients were discharged on no antiarrhythmic drugs compared to 84% after AV-node ablation. In addition, PVI patients frequently underwent re-do procedures. 20% had undergone a re-ablation 1 year after the index procedure compared to 3% of AVN-ablation patients. Of note, the index procedure was not the first ablation in 18% of PVI patients. In addition to individual disadvantages in case of complications, re-hospitalizations, and re-do procedures, PVI and re-do procedures as well as hospitalizations likely add up to significant financial burden to the healthcare system.

Is AV-node ablation the easier and less cost-intensive way to achieve symptomatic improvement? This is likely a too simple conclusion from these registry data. In a randomized study comparing PVI and AV-node ablation in combination with cardiac resynchronization in patients with heart failure, PVI was superior to AVN-ablation despite sufficient rate control and biventricular pacing [9]. Recent randomized studies in heart failure patients have shown a prognostic benefit from PVI vs. conventional therapy [13]. In addition, long-term complications of device therapy have not been evaluated in this registry but are well known from other studies. It is also less clear whether younger patients would have the same symptomatic improvement from AVN-ablation and pacemaker treatment as older patients. This has already been questioned in context of previous studies comparing rate and rhythm control [4–6], but data are sparse. A recent study comparing rate and rhythm control drugs in patients younger than 65 years reported no difference in heart failure and non-cardiovascular hospitalizations while hospitalizations for cardiovascular reasons were more frequent with rhythm control [11].

It is still unclear whether successful treatment of AF by means of PVI has prognostic impact by reducing AF-related morbidity and mortality. A large Swedish registry [14] and a propensity score-matched analysis from Israel with almost 4000 patients [15] revealed a potential prognostic benefit of PVI. Two prospective randomized trials (EAST trial and CABANA trial) have been initiated to shed light onto this question [16, 17]. While EAST is still underway, results of CABANA have recently been presented. This randomized, multicenter trial investigated whether primary catheter ablation with the goal to eliminate AF was superior to drug therapy (either for rate or rhythm control) with respect to safety and efficacy. 2204 patients were included. At 5 years, the primary outcome death, disabling stroke, serious bleeding, or cardiac arrest was not significantly different (8% vs. 9.2%, $p = 0.3$). However, there was a significant reduction of the combined predefined secondary endpoint of death or

cardiovascular hospitalization (51.7% vs. 58.1% for ablation vs. drug therapy, $p = 0.002$) as well as AF recurrence rate with ablation (time to first AF recurrence: HR 0.53, $p < 0.0001$). Crossover rates were high and can confound assessment of the various endpoints. Of note, the as-treated analysis demonstrated superior efficacy of ablation for the primary cardiovascular outcome ($p = 0.006$). Likewise, for heart failure patients, rhythm control with PVI may be superior to rate control based on recent data of the CASTLE-AF trial [13].

CABANA and CASTLE-AF suggest a prognostic benefit from PVI, but more data and further analysis are required to understand the observations and characterize patients who benefit most from either treatment strategy. A subgroup analysis of CABANA revealed that PVI is superior in patients < 65 years, and drug therapy better in patients ≥ 75 years. Certainly, treatment has to be tailored to the individual patient. However, our observations reveal the limitations of PVI in a large real-world catheter ablation cohort and should remind to consider AV-node ablation probably more often. For those who failed PVI and antiarrhythmic drug therapy, the number of re-do procedures should probably be limited, particularly after proof of isolated pulmonary veins until a convincing treatment concept is established for additional ablation lesions. So far, several randomized studies have not shown superiority of additional ablation lines and substrate ablation over pure PVI [18–21].

Limitations

This study has several limitations; many related to the data analyzed stemming from a clinical registry as opposed to a randomized trial. The results should be interpreted in a descriptive, not in a confirmatory sense. The ablation strategy was left to the investigator's preference and not standardized. The indication for AVN ablation and PVI was also left to the investigators decision. While this reflects "real-world" clinical decision making at least in the participating centers, it was associated with profound differences between the patient populations. Participation in the registry was voluntary and not all consecutive patients from a given center may have been included. Selection bias and reporting bias are, therefore, possible limitations. Details on previous ablations and procedures performed after the index ablation were not available (e.g., reconnection at the time of the redo procedure), and some information that might be of interest has not been recorded (e.g., indication for the procedure, details of previous ablations, complications, circumstances of sudden death). In addition, patients treated up to 2010 were enrolled. Since then ablation strategies and technologies have changed significantly, likely influencing some of the parameters and outcomes presented (e.g., procedure duration, fluoroscopy time, complication rates).

Conclusion

AV-node ablation is performed much less frequently than PVI for symptomatic treatment of AF and typically in older patients with more comorbidities. This mirrors current guideline recommendations. Symptomatic improvement was similar in both groups (including a re-ablation in 20% of PVI patients) and was achieved in about 80% of patients. Hospitalization for cardiovascular reasons was lower in the AVN group than in the PVI group despite older age and more cardiovascular comorbidities. From the present data no conclusive evidence about a possible prognostic benefit from PVI, as suggested by recent prospective randomized studies, can be drawn. Further analysis and additional studies are needed to identify patients who benefit the most from either strategy.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

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