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Catheter Ablation Versus Antiarrhythmic Medication in Patients with Atrial Fibrillation: a Propensity-Matched Analysis Based on a German Claims Data Set

Antje Mevius[1], Thomas Wilke[1,*], Andreas Fuchs[2],Angela Kloppenburg[3], Susanne Engel[3], Roland Linder[3], Günter Breithardt[4]

[1]Institute of Pharmacoeconomics and Pharmaceutical Logistics (IPAM), Wismar University, Germany
[2]AOK PLUS, Dresden, Germany
[3]Techniker Krankenkasse (Hamburg, Germany)
[4]Department of Cardiovascular Medicine, Division of Electrophysiology, University Hospital Münster, and Atrial Fibrillation Network e.V. (AFNET), both in Münster, Germany

*Corresponding author: Thomas Wilke, Institute of Pharmacoeconomics and Pharmaceutical Logistics (IPAM), Wismar University, Germany; Tel: 0049-3841-8ß758-1014; Email: Thomas.wilke@ipam-wismar.de

Abstract

Aims: Main objective of our analysis was to assess the long-term clinical and health economics outcomes of catheter ablation versus antiarrhythmic medication therapy in Germany.

Methods: We conducted a retrospective analysis of anonymized claims data covering the years 2010-2014. Patients with at least one diagnosis of AF and a minimum follow-up period of twelve months (excluding death) were included and assigned into two treatment groups: AF ablation and antiarrhythmic medication. To balance different patient characteristics in both groups, the final analysis was based on propensity score-matched (PSM) cohorts.

Results: Of 498,253 AF patients, 2,404 could be assigned to the final analysis population – 1,202 patients in each group. The difference in the all-cause mortality rate reached statistical significance after 24 months of observation (1.5% versus 3.1% (p=0.015)) and after 36 months (1.7% versus 4.8% (p=0.005)). We could not identify any significant difference between the groups in cardiovascular events (amongst others stroke, TIA, myocardial infarction) over the three-year observation period. Direct cardiology-associated healthcare costs after index date (excluding catheter ablation procedure) were significantly different between the groups in the first and third observational year (third-year costs of €1,618 in the ablation group versus €2,462 in the medication group; p<0.007).

Conclusion: Over a period of 36 months, all-cause mortality in AF patients who underwent catheter ablation was found to be significantly lower compared to AF patients who received antiarrhythmic medication. Direct cardiology healthcare costs after the ablation procedure proved to be consistently and significantly lower in comparison with medication therapy.

Keywords: Atrial fibrillation; Catheter ablation; Antiarrhythmic medication

Abbreviations: AF: Atrial fibrillation; ATC: Anatomical Therapeutic Chemical; DRG: Diagnosis Related Groups (classification of hospital cases for reimbursement puposes); ICD: implanted cardioverter defibrillator ICD-10: International Statistical Classification of Diseases; OPS: Operationen- und Prozedurenschlüssel (operation and procedure codes); KM: Kaplan-Meier

Introduction

Atrial fibrillation (AF) is the most common significant cardiac rhythm disorder [1]. It is associated with substantial morbidity and mortality from stroke and thromboembolism [1,2]. An effective and important treatment option for many AF patients is catheter ablation [3–5]. Clinical trials have shown that catheter ablation (as a second-line or even first-line treatment option) maintains sinus rhythm more effectively than antiarrhythmic medication [6–10]. However, most of these trials were based on small samples of patients who were treated in specialized centres, and the follow-up periods on which the studies were based were short.

Consequently, the potential health benefits of catheter ablation in terms of long-term real-world cardiovascular outcomes such as stroke, TIA, myocardial infarction and/or systemic non-CNS embolism have been demonstrated only rarely. Similarly, little is known with regard to the long-term health-economic evaluation of catheter ablation in a real-world scenario. A published study with data from Swedish health registries compared propensity-matched cohorts of ablated with non-ablated AF patients: ablation was associated with lower risk of ischemic stroke and lower mortality risk [11]. Another one of the rare analyses in this respect, a US claims data-based analysis of propensity-matched samples of AF patients who either underwent catheter ablation or received antiarrhythmic medication concluded that catheter ablation patients had a significantly lower risk of stroke, TIA and heart failure-associated hospitalizations [12].

Building on the methodology developed in the publication cited above, the main objective of our analysis was to assess the long-term clinical and health economics outcomes of catheter ablation versus antiarrhythmic medication therapy in Germany.

Methods

Sample

We conducted a retrospective analysis of anonymized claims data which were provided by two German statutory health insurance (SHI) funds- AOK PLUS and Techniker Krankenkasse (TK). Both SHI funds together insure 13 million people: more than 17% of the statutorily insured population in Germany. The database covered the years 2010-2014 and included information on patients' demographics, outpatient treatments (diagnosis codes and visits to general practitioners and/or specialists), inpatient treatments (dates, diagnoses, procedures, length of stay) and claims filled for prescription medications.

A patient was included in our analysis if at least one outpatient or inpatient diagnosis of AF was recorded during the inclusion period from 01/01/2010 to 31/12/2013 (until 2012: ICD10-Code I48.1-; in 2013: ICD10-Code I48.0-/I48.1-/I48.2-). For all patients, the minimum follow-up period was defined as twelve months; only in case of death, this period was shorter.

We divided the patients into two groups. Those who had undergone catheter ablation in the left atrium between 2011 and 2013 were assigned to the AF ablation group. Patients who received at least two prescriptions for at least two different antiarrhythmic agents in at least one of the antiarrhythmic drug classes Ia, Ic or III (according to the Singh Vaughan Williams classification) were assigned to the antiarrhythmic medication group (the detailed algorithm for group assignment is available in Supplemental Figure 1). Information about the prescribed dosages were not reported within the claims dataset. Since prescriptions for two different antiarrhythmic drugs were mandatory in this group, one requirement was that these patients had experienced at least one antiarrhythmic drug treatment failure. If a patient underwent catheter ablation treatment between 2010 and 2013, but had received prescriptions of two antiarrhythmic medications before that procedure, he/she was assigned to the ablation group. The start date (index date) of observation for the ablation group was the date of the ablation procedure; for the medication group, the start date was the date of the first observed prescription of the second antiarrhythmic agent. All patients were followed for a period of twelve months and, in subsets, for a period of 24/36 months, whichever their enrolment allowed.

Patients were generally excluded if at least one of the following criteria was fulfilled, based on the respective procedure codes:

- catheter ablation in the left atrium in 2010, or

- ablation in the right or left ventricles during the entire study period, or

- open (surgical) ablation procedure or atrioventricular junction ablation during the same hospital stay as used for the AF ablation, or

- valvular (interventional or surgical) procedure before index date, or

- pacemaker or cardioverter defibrillator (ICD) implantation before index date.
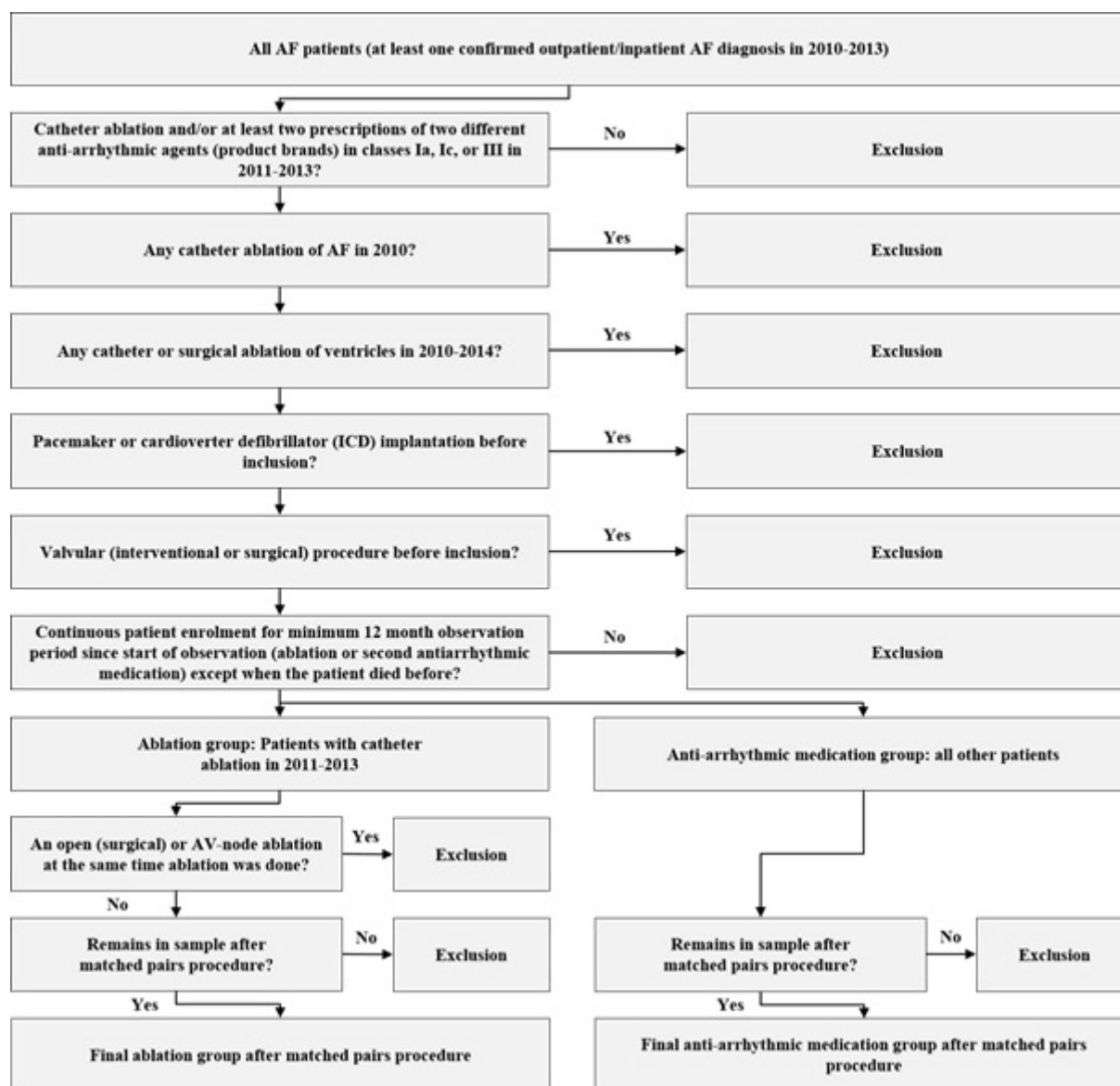
Supplemental Figure1: Detailed inclusion and exclusion criteria for the ablation and medication group

To reduce the risk of bias resulting from different patient characteristics in both groups, the final analysis population was defined based on propensity score-matched (PSM) cohorts. We applied a logistic regression model to calculate each patient's propensity score as the probability of being treated with ablation versus drug therapy, given the individual patient characteristics which were based on a twelve-month baseline period before the index date. Sixteen different characteristics, such as patient demographics, comorbid conditions and resource use, were used as potential independent predictor variables. Eight variables were found to be significantly associated with the probability of belonging to one of the groups, based on a backward stepwise elimination (p=0.05 cut-off) methodology: age and care level at index date, rhythm and rate control medication use (ATC-codes: C01BA-/C01BB-/C01BC-/C07AB-/C07AG-/C01BD-/C08-/C01AA-/C01EB17 or C01EB10), anti-coagulant use, insulin use, occurrence of ischemic stroke, all-cause medication costs, and hospitalization costs in the baseline period. The care level from 1-3 in case of needed day care is specified as follows: 1=no help needed for daily-life activities with an extent of at least 90 minutes per day, 2=care needed for at least 3 hours per day; 3=care needed for at least 5 hours per day. Variables excluded from the final PSM due to their insignificance were: gender, antihypertensive medication use, use of oral antidiabetic medication, occurrence of hemorrhagic stroke, occurrence of TIA, occurrence of myocardial infarction. Patients were matched 1:1 within gender-specific 5-years age groups, based on their propensity score with a maximum allowable difference of 0.001.

Outcomes

The following outcomes were defined (all referring to either 12/24/36 months of patient-specific observation); events were considered only if they led to an inpatient hospital stay. Detailed information regarding event definition is available in Supplemental Table 1.

- Primary outcome
o All-cause death and/or occurrence of TIA/ stroke as composite outcome
- Secondary outcomes
o Occurrence of all-cause death
o Occurrence of stroke
o Occurrence of TIA
o Occurrence of heart failure/myocardial infarction
o Occurrence of arterial embolism
o Occurrence of ICD/pacemaker implantation
o Occurrence of hospital admission for syncope
o Occurrence of hospital admission for cardiac arrhythmias hospitalizations with atrial fibrillation were excluded,be cause long-termcheck-ups following the ablation itself were not to be counted as negative events)
o Occurrence of any of the outcomes defined above (as composite outcome II)
o Patient-related cardiology costs after index date including:
o Hospitalization costs related to the secondary outcomes defined above (the initial ablation procedure is not included)
o Medication costs for cardiology medications (ATC-Code C-)
o Ambulant visits to cardiologists or neurologists
o Rate of pneumonia (pneumonia leading to hospital admission; identification by ICD-10 codes J12.-/J13.-/J14.-/J15.-/J16.-/J17.-/J18.-). This rate was analyzed and compared to assess the quality of the PSM procedure.

Outcome	Codes	Description
TIA	G48.8/G45.9	Transient cerebral ischaemic attack
Stroke	I60.-	Subarachnoid haemorrhage
	I61.-	Intracerebral haemorrhage
	I62.-	Other nontraumatic intracranial haemorrhage
	I63.-	Cerebral infarction
	I64.-	Stroke, not specified as haemorrhage or infarction
Heart failure/ Myocardial infarction	I09.9	Rheumatic heart disease
	I11.-	Hypertensive heart disease
	I13.-	Hypertensive heart and renal disease
	I50.-	Heart failure
	I21.-	Acute myocardial infarction
	I22.-	Subsequent myocardial infarction
Arterial embolism	G45.3	Amaurosis fugax
	H34.-	Retinal vascular occlusions
	I26.-	Pulmonary embolism
	K55.0	Mesenteric embolism
ICD/pacemaker implantation	OPS 5-377/5-378	Implantation procedures
	DRG F12	
Syncope	R55.-	Syncope and collapse
Cardiac arrhythmias	I47.-	Paroxysmal tachycardia
	I48.0 (valid until 31/12/2012) I48.3/I48.4 (valid from 01/01/2013)	Atrial flutter
	I49.-	Other cardiac arrhythmias

Supplemental Table 1: Definition primary/secondary outcomes

Statistical analysis

All statistical analyses were done with MySQL and SPSS (most current versions). Comparisons of event rates between treatment groups were performed with Fisher's exact test or t-test. For our primary outcome, we additionally plotted a Kaplan-Meier curve and compared time to event as well as the percentage of event-free patients over time between groups with the log-rank test, based on an unadjusted Cox regression analysis.

The application of inclusion and exclusion criteria, propensity score-based matching procedure, identification of events and cost calculation were conducted separately for the two datasets. The results were aggregated and statistically analyzed.

Due to the anonymized nature of the used dataset, no ethical approval was needed. However, the study protocol was reviewed and approved by a Scientific Steering Committee to which all authors belonged.

Results

Sample characteristics

In total, 498,253 AF patients were identified (54.4% AOK PLUS, 45.6% TK) (Table 1). The inclusion criteria for the two patient groups were met by 8,334 patients (ablation group) and 3,576 patients (medication group). After the exclusion criteria had been applied, 4,240 patients remained in the ablation group and 2,598 patients in the medication group. The final analysis population resulting from the PSM consisted of 2,404 patients – 1,202 patients in each group (12.5% AOK PLUS, 87.5% TK; Figure 1, Table 1). Mean age was 64.12 years in the ablation group and 64.98 years in the medication group, 61.2% and 64.1% of the patients were female. The mean follow-up time since index date was 935.5 days (2.6 years) in the ablation group, and 959.7 days (2.6 years) in the medication group. Within the ablation group, 956 patients (79.5%) could be observed for a period of at least 24 months, and 530 patients (44.1%) for at least 36 months. In the medication group, this applied to 987 patients (82.1%) and 629 patients (52.3%) (Table 1).

	Dataset: AOK Plus		Dataset: TK		Combined datasets	
	Ablation group	Medication group	Ablation group	Medication group	Ablation group	Medication group
Number of all identified patients	905	638	3,335	1,960	4,240	2,598
Number of patients after propensity score matching (PSM)	150	150	1,052	1,052	1,202	1,202
observable for at least 24 months	92	111	864	876	956	987
observable for at least 36 months	32	65	498	564	530	629
Average observational period (days)	818.47	936.93	952.23	962.96	935.54	959.71
Mean age in years [1]	67.81	67.57	63.60	64.61	64.12	64.98
Gender, n (%) *Male*	71 (47.33%)	78 (52.0%)	664 (63.12%)	693 (65.87%)	735 (61.15%)	771 (64.14%)
Female	79 (52.67%)	72 (48.0%)	388 (36.88%)	359 (34.13%)	467 (38.85%)	431 (35.86%)

Table 1: Descriptive characteristics of included AF patients
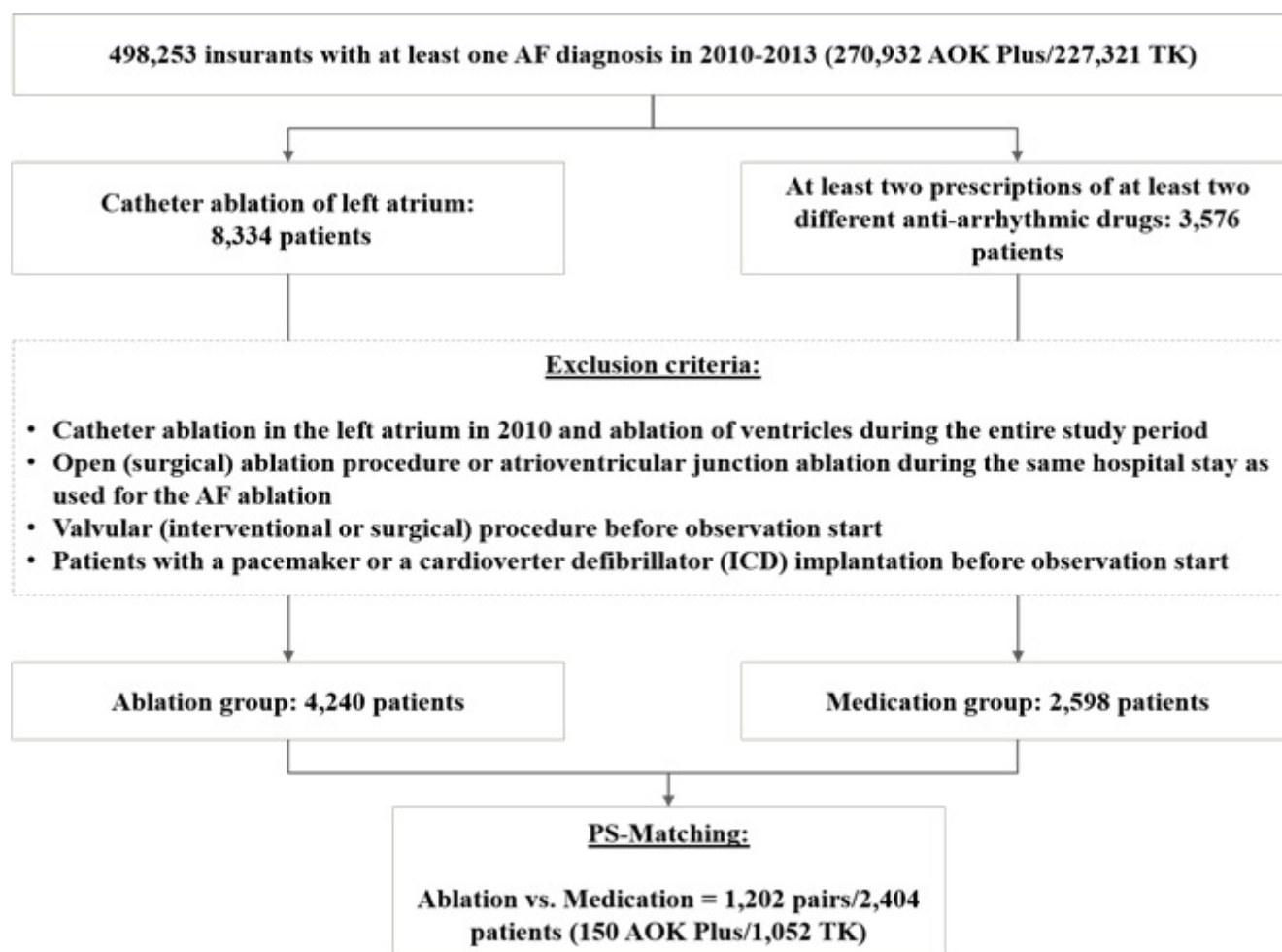1 Based on index date (start of observation).

Figure 1: Sample definition

Primary objective

After twelve months from index date, 34 patients suffered a stroke or a TIA or died: this concerned 13 patients in the ablation group (1.1%) and 21 patients in the medication group (1.8%). The difference was not significant (p=0.226; Table 2). After 24 months, the rate was 2.7% in the ablation group and 4.0 % in the medication group (p=0.165; Table 2). After 36 months of observation, the rate was significantly lower in the ablation group: 3.6% versus 6.2 % (p=0.043; Table 2). Via Kaplan-Meier estimation (log-rank: p=0.042), the significant difference after 36 months of observation between the ablation group (96.4% of observed patients were event-free) and the medication group (93.8% of observed patients were event-free) could be confirmed (Figure 2).

Secondary study objectives

All-cause mortality rate after twelve months was 0.6% (7 patients) in the ablation group and 1.3% (16 patients) in the medication group (p=0.092). The difference between the groups increased over time and reached statistical significance after 24 months of observation (1.5% versus 3.1% (p=0.015)) and after 36 months (1.7% versus 4.8% (p=0.005; Table 2)).

Event rates for stroke, TIA, heart failure/myocardial infarction, arterial embolism, pacemaker/ICD implantation and syncope were almost evenly distributed between the compared groups; none of the observed differences reached statistical significance (Table 2).

Hospitalizations due to cardiac arrhythmias (AF was excluded) during the twelve months of follow-up were observed for 56 patients (4.7%) in the ablation group and 32 patients (2.7%) in the medication group (p=0.009). After 24 months, this rate was 6.6% versus 3.7% (p=0.003), and after 36 months the difference between the two groups was no longer significant (8.1% versus 5.9%; p=0.136). Accordingly, the event rates with regard to composite outcome II were not significantly different between the groups (8.5% versus 6.8% after 12 months; 12.3% versus 11.0% after 24 months, and 16.4% versus 18.0% after 36 months; Table 1, Table 2).

Objectives	Observation period[1]	Ablation group	Medication group	p-value[2]
Composite outcome I[3]	12 months (%)	13 (1.08%)	21 (1.75%)	0.226
	24 months (%)	26 (2.72%)	39 (3.95%)	0.165
	36 months (%)	*19 (3.58%)*	*39 (6.20%)*	***0.043***
Death	12 months (%)	7 (0.58%)	16 (1.33%)	0.092
	24 months (%)	14 (1.46%)	31 (3.14%)	***0.015***
	36 months (%)	9 (1.70%)	30 (4.77%)	***0.005***
Stroke	12 months (%)	4 (0.33%)	4 (0.33%)	1
	24 months (%)	8 (0.84%)	7 (0.71%)	0.800
	36 months (%)	9 (1.70%)	10 (1.59%)	1
TIA	12 months (%)	2 (0.17%)	1 (0.08%)	1
	24 months (%)	4 (0.42%)	1 (0.10%)	0.211
	36 months (%)	2 (0.38%)	1 (0.16%)	0.596
Myocardial infarction	12 months (%)	28 (2.33%)	21 (1.75%)	0.387
	24 months (%)	32 (3.35%)	32 (3.24%)	0.900
	36 months (%)	31 (5.85%)	27 (4.29%)	0.279
Arterial embolism	12 months (%)	2 (0.17%)	4 (0.33%)	0.687
	24 months (%)	5 (0.52%)	5 (0.51%)	1
	36 months (%)	3 (0.57%)	7 (1.11%)	0.360
Pacemaker / ICD	12 months (%)	11 (0.92%)	15 (1.25%)	0.555
	24 months (%)	13 (1.36%)	22 (2.23%)	0.389
	36 months (%)	15 (2.83%)	22 (3.50%)	0.616
Syncope	12 months (%)	1 (0.08%)	5 (0.42%)	0.218
	24 months (%)	4 (0.42%)	7 (0.71%)	0.548
	36 months (%)	4 (0.75%)	11 (1.75%)	0.192
Cardiac arrhythmia	12 months (%)	56 (4.66%)	32 (2.66%)	***0.009***
	24 months (%)	63 (6.59%)	36 (3.65%)	***0.003***
	36 months (%)	43 (8.11%)	37 (5.88%)	0.136
Composite outcome II[4]	12 months (%)	102 (8.49%)	82 (6.82%)	0.125
	24 months (%)	118 (12.34%)	109 (11.04%)	0.373
	36 months (%)	87 (16.42%)	113 (17.97%)	0.487
Cardiology costs[5]	Ø costs per patient in 12 months	€576.35	€718.56	***0.045***
	Ø costs per patient in 24 months	€1,085.71	€1,403.63	0.051
	Ø costs per patient in 36 months	€1,618.41	€2,462.15	***0.007***
Pneumonia	12 months (%)	6 (0.50%)	4 (0.33%)	0.753
	24 months (%)	8 (0.84%)	8 (0.81%)	1
	36 months (%)	7 (1.32%)	8 (1.27%)	1

Table 2: Observed event rates and costs

[1] % in 12 months based on N=1,202/1,202;% in 24 months based on N=956/987; % in 36 months based on N=530/629

[2] p-value: Fisher's exact Test/t-Test (costs); significant values are highlighted

[3] Composite Outcome I: death and/or occurrence of TIA and/or stroke

[4] Composite Outcome II: patient was affected byany of the secondary events (death/stroke/TIA/myocardial infarction/arterial embolism/pacemaker surgeries/syncope/cardiac arrhythmia)

[5] Cardiology-caused costs: inpatient costs with diagnoses referred to eventdefinition, medication costs with ATC-Codes C- and outpatient costs (only visits at cardiologist or neurologist)
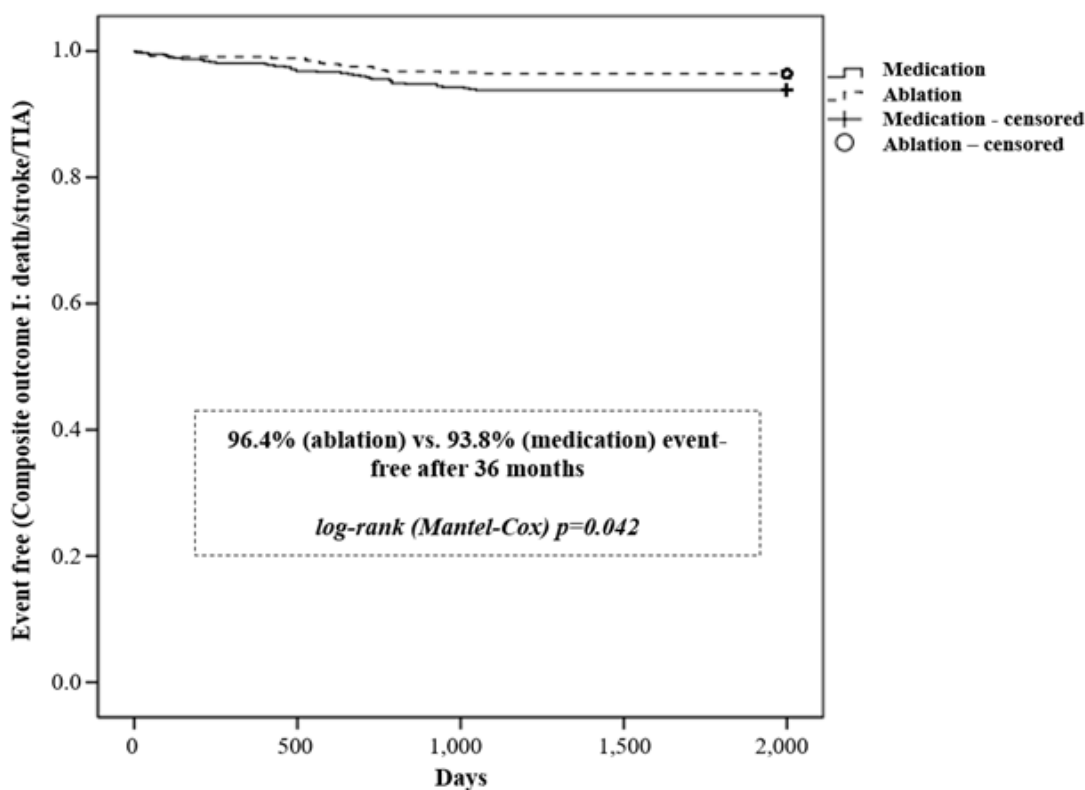
Figure 2: Kaplan-Meier curve of the time to first event (Composite outcome I: death/stroke/ TIA); only patients with a 36 months' follow-up period were included (N=530/629)

The analysis of direct cardiology-associated healthcare costs after index date per patient-year indicated a significant difference between the ablation group and the medication group in the first and third observational year (third-year costs of €1,618 in the ablation group versus €2,462 in the medication group; p<0.007; Table 2). In this respect, outpatient costs did not differ between both groups across the observation period. Medication costs decreased during the three years in both groups but were consistently higher (by a factor of 1.91, 2.03, and 2.17, respectively) in the medication group than in the ablation group (Figure 3). This difference was partly offset by higher hospitalization costs in the ablation group in the first two observational years (additional costs of €103 in the first year and €88 in the second year). However, direction changed in this respect in the third year, with €32 of additional hospitalization costs in the medication group.

Finally, the event rate for pneumonia was found to be nearly identical between the two groups in all tested follow-up intervals. This indicates that the quality of our matching procedure was reasonable.

Discussion

Rhythm control therapy is an essential part of AF management. Antiarrhythmic medication is the first choice for restoring sinus rhythm to improve symptoms in AF patients who remain symptomatic on adequate rate control therapy. In addition, catheter ablation has become established over time as a common treatment option for patients with symptomatic paroxysmal and persistent AF [4,5]. However, the effect of rhythm control via different treatment options on the reduction of major cardiovascular event risk in real-world contexts has not been investigated broadly and is therefore under investigation[13,14]. Our study contributes to this research. Its main strengths were absence of any patient selection bias or cluster effects that may have influenced previous studies. Furthermore, we covered an exceptionally large sample of German patients.

Future research might consider new technologies like MRI-guided catheter ablation or MRI driven characterization of fibrotic tissue. Potentially, future studies will compare competing therapies stratified by the burden of fibrotic tissue.
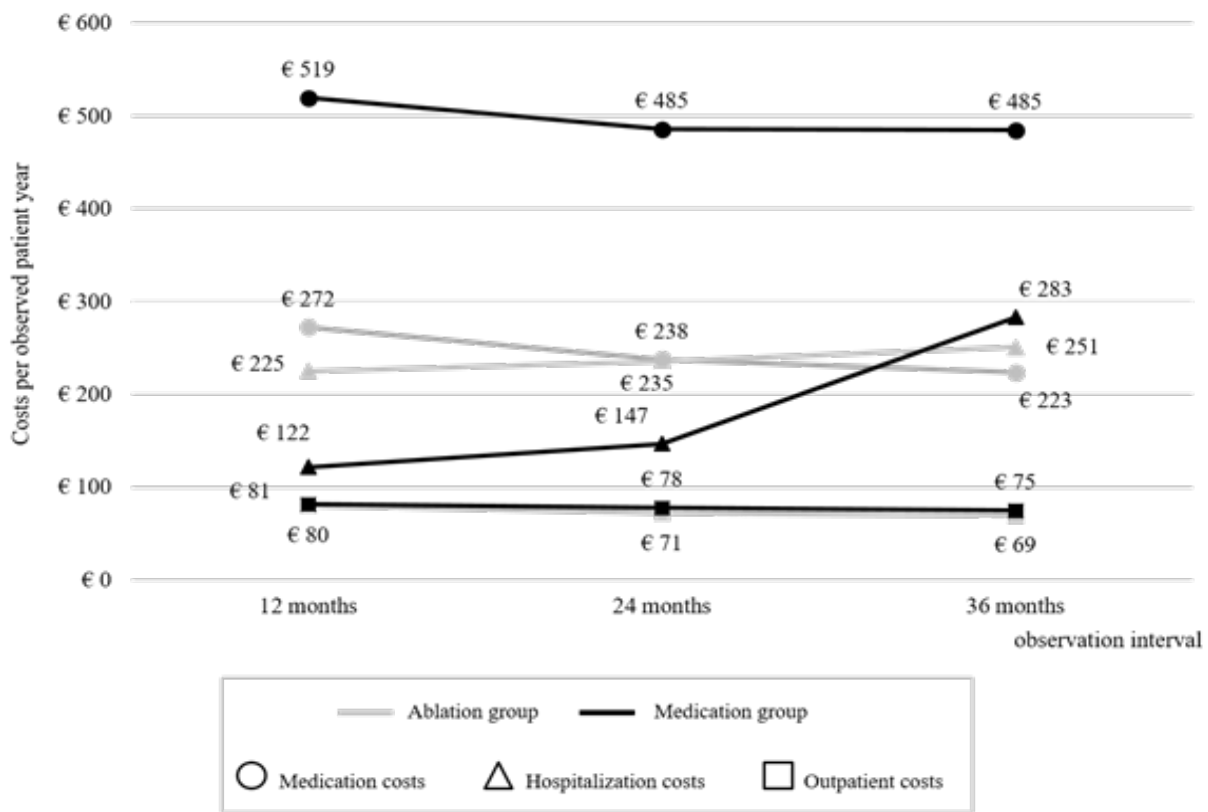
Figure 3: Development of costs per observed patient year, separately for medication, hospitalization and outpatient costs

In our propensity score-matched comparison of AF patients who received either catheter ablation or at least two different antiarrhythmic drug medications, we identified lower all-cause mortality in the catheter ablation group. The mortality rate for patients treated with antiarrhythmic medication was 2.2 times higher than that of patients in the ablation group after 24 months, whereas it was 2.8 times higher after 36 months. This finding is in line with three previous studies that reported (1) a 56% relative risk reduction for mortality in patients receiving catheter ablation versus patients receiving amiodarone for the treatment of persistent AF in patients with heart failure (a multicentre randomized study with 2-year follow-up; log-rank p=0.037) [8], (2) catheter ablation was associated with lower mortality risk (propensity score matched samples of ablated vs. non-ablated AF patients, data from Swedish registries; HR 0.50, 95% CI 0.37-0.62) [11] and (3) death rate to be significantly lower in the ablation cohort (0.5% per patient-year) compared with the medically treated cohort in the Euro Heart Survey[15].

In contrast to the results reported by Friberg et al. [11], Reynolds et al. [12] and Chang et al. [16], differences between event rates with stroke/TIA, myocardial infarction/heart failure and arterial embolism were not statistically significant between the treatment groups. We assume that, due to the strict definitions and despite the large datasets, our sample sizes and the associated frequency of event occurrence may not have been high enough.

Regarding direct cardiology healthcare costs, our data show significantly lower follow-up costs in the ablation group in comparison with the medication group. These results confirm the findings of other previous studies [17,18]. The main driver of this cost difference is higher medication costs in the medication group and, additionally in the third observational year, higher hospitalization costs in that group. Interestingly, additional costs in the medication group are not driven by hospitalization frequency among those patients, but by higher costs per hospitalization, indicating a higher severity of cardiovascular events in the medication group.

It needs to be noted that our cost analysis only covered follow-up costs. This means that it did not include costs for the index ablation treatment in the ablation group. Reported costs in this respect vary widely, depending on type and modalities of the procedure and patient-individual risk factors. European studies

have reported initial ablation costs varying between €4,715 [17] and €9,600 [19]. These costs are not offset by the reported cost reductions due to catheter ablation as reported in our study if only a three-year follow-up is observed.

We acknowledge some limitations of our study. First, since our dataset provided only limited information, we could not analyze all aspects and potential effects of catheter ablation on clinical/health-economic outcomes. So, for example, quality of life as an important outcome could not be observed. In this respect, previous studies have shown a superiority of catheter ablation to conventional antiarrhythmic medication therapy [9,18].

Second, the underlying data were primarily collected for financial claims and not gathered specifically for research purposes, which is a general weakness associated with claims-based data studies. Limitations are present in both the level of detail and precision. Despite these weaknesses, a review of existing investigations shows that claims-based data sets can be used as valid research data [20]. Nevertheless, we cannot exclude a possible indication bias related to unknown and/or concealed confounders. In relation to that, additional patient characteristics that could not be incorporated in our PSM procedure could have influenced our results. So, proof of the superiority of catheter ablation in comparison with antiarrhythmic medication needs to be provided by prospective randomized controlled trials, such as the CABANA study which analyzed a composite outcome of all-cause death, disabling stroke, severe bleeding and cardiac arrest between randomized AF populations who received either ablation or antiarrythmic medication. To the knowledge of the authors, CABANA showed that above composite outcome did not differ significantly between ablated patients compared to those treated medically, based on an "intention-to-treat" analysis [21].

In summary, over a period of 36 months, all-cause mortality in AF patients who underwent catheter ablation was found to be significantly lower compared to AF patients who received antiarrhythmic medication. We could not identify any significant difference between the groups in the defined cardiovascular events over the three-year observation period. Direct cardiology healthcare costs after the ablation procedure proved to be consistently and significantly lower in comparison with medication therapy, excluding the index ablation procedure. Our study does not provide any detailed recommendation for the decision when to use choose catheter ablation procedures instead of medication therapy. However, the ongoing discussion around criteria in this respect which are related to relevant concepts such as the risk of fibrotic scars related to multiple ablation procedures, the uselessness of AF ablation in patients with low left ventricular ejection fraction, the impairment of left atrial strain as a consequence of repeated AF ablation procedures, etc. shows that substantial research needs to be done to derive optimal treatment concepts [22].

Disclosure

Funding

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