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The cost-effectiveness of radiofrequency catheter ablation as first-line treatment for paroxysmal atrial fibrillation: results from a MANTRA-PAF substudy

Mattias Aronsson[1]*, Håkan Walfridsson[2], Magnus Janzon[2], Ulla Walfridsson[2,3], Jens Cosedis Nielsen[4], Peter Steen Hansen[4], Arne Johannessen[5], Pekka Raatikainen[6], Gerhard Hindricks[7], Ole Kongstad[8], Steen Pehrson[9], Anders Englund[10], Juha Hartikainen[11], Leif Spange Mortensen[12], and Lars-Åke Levin[1]

[1]Department of Medical and Health Sciences, Linköping University, Linköping, Sweden; [2]Department of Cardiology and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden; [3]Department of Medical and Health Sciences, Division of Nursing Science, Linkoping University, Linkoping, Sweden; [4]Department of Cardiology, Aarhus University Hospital, Skejby, Denmark; [5]Gentofte University Hospital, Copenhagen, Denmark; [6]Heart Center Co., Tampere University Hospital, Tampere, Finland; [7]Leipzig University Hospital, Leipzig, Germany; [8]Lund University Hospital, Lund, Sweden; [9]Rigshospitalet, Copenhagen, Denmark; [10]University Hospital, Örebro, Sweden; [11]Heart Center, Kuopio University Hospital, Kuopio, Finland; and [12]Danish Information Technology Centre for Education and Research, Aarhus, Denmark

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Aim The aim of this prospective substudy was to estimate the cost-effectiveness of treating paroxysmal atrial fibrillation (AF) with radiofrequency catheter ablation (RFA) compared with antiarrhythmic drugs (AADs) as first-line treatment.

Methods and results A decision-analytic Markov model, based on MANTRA-PAF (Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation) study data, was developed to study long-term effects and costs of RFA compared with AADs as first-line treatment. Positive clinical effects were found in the overall population, a gain of an average 0.06 quality-adjusted life years (QALYs) to an incremental cost of €3033, resulting in an incremental cost-effectiveness ratio of €50 570/QALY. However, the result of the subgroup analyses showed that RFA was less costly and more effective in younger patients. This implied an incremental cost-effectiveness ratio of €3434/QALY in ≤50-year-old patients respectively €108 937/QALY in >50-year-old patients.

Conclusion Radiofrequency catheter ablation as first-line treatment is a cost-effective strategy for younger patients with paroxysmal AF. However, the cost-effectiveness of using RFA as first-line therapy in older patients is uncertain, and in most of these AADs should be attempted before RFA (MANTRA-PAF ClinicalTrials.gov number; NCT00133211).

Keywords Atrial fibrillation • Radiofrequency ablation • Anti-arrhythmic drugs • Cost-effectiveness

Introduction

Atrial fibrillation (AF) is a common type of arrhythmia[1] that is defined by an irregular and often rapid heartbeat. It is associated with high costs, increased mortality, and a reduced quality of life.[2,3]

Atrial fibrillation can be categorized into paroxysmal (PAF), persistent, long-standing persistent, and permanent AF. According to the national and international guidelines, radiofrequency catheter ablation (RFA) should be considered in patients with symptomatic paroxysmal or persistent AF who do not respond to antiarrhythmic drugs (AADs).[4]

Previous studies have proved that RFA in patients who failed at least one AAD is both clinically efficient[5–8] and cost-effective in multiple risk groups.[9–13]

It has been suggested that RFA can be used as first-line treatment of paroxysmal atrial fibrillation (PAF), due to its better efficiency and

* Corresponding author. Tel: +46 736 219021; fax: +46 101034995. *E-mail address*: mattias.aronsson@liu.se

fewer serious side effects than AADs.[4,6,12] Previously published studies of such implementation have been based on either a limited number of patients[14] or conducted at a single centre,[15] which makes it difficult to draw general conclusions. In the multicentre MANTRA-PAF (Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation) trial, patients with PAF were randomized to RFA or AAD therapy at the early phase of the disease and were followed for 24 months.[16]

This prospective substudy aimed to estimate the cost-effectiveness of RFA as first-line treatment of PAF compared with AAD.

Methods

Analytical approach

Our prospective analysis followed a model approach based on the 2-year follow-up data of the MANTRA-PAF trial. For long-term extrapolation, the MANTRA-PAF results were complemented with data from clinical studies and registers. A lifelong Markov model was developed to calculate the incremental cost-effectiveness ratio for RFA as first-line treatment in a hypothetical cohort of patients with PAF. Sensitivity analyses were done both probabilistically and deterministically. The probabilistic analysis to study statistical uncertainty was made using Monte-Carlo simulations. Model structure uncertainty was studied in deterministic one-way sensitivity analyses by varying values of parameters and assumptions.

Target populations

This cost-effectiveness analysis had the MANTRA-PAF study population as a starting point and base-case scenario. The MANTRA-PAF trial was conducted at 10 centres located in Denmark, Finland, Germany, and Sweden, and the data used for this analysis were collected prospectively. Patients with at least two documented episodes of symptomatic AF within the preceding 6 months were eligible to the study. Exclusion criteria were previous episodes of AF >7 days without spontaneous termination or cardioversion, age >70 years, previous or ongoing treatment with Class IC or Class III AAD, contraindication to Class IC and Class III agents, previous ablation for AF, left atrial diameter >50 mm, left ventricular ejection fraction <0.40, contraindication to oral anticoagulation, moderate-to-severe mitral valve disease, severe heart failure, expected surgery for structural heart disease and secondary AF.[17] A total of 294 patients were randomized, of which 286 received the assigned treatment.[16]

Limited medical treatment options exist for patients with AF. The current study hypothesized that due to the poor efficacy and frequent adverse effects, young patients (≤ 50 years) would be difficult to treat with AADs and thereby be more severely affected by AF, if the first AAD failed. Age has been previously highlighted as an important aspect for the effectiveness of RFA treatment.[16,18] The age of 50 years was chosen as the cut-off point in our subgroup analysis. Clinical efficacy and costs were compared between 76 patients (26%) of up to 50 years of age and 218 patients (74%) aged >50 years (baseline characteristics in Supplementary material).

Model structure and assumptions

To study the use of RFA as a first-line treatment compared with AAD, a dynamic lifelong model was developed in Excel (Microsoft, Redmond, WA). The cycle length was 1 month, and the short-term model was repeated until all patients had died. As shown in *Figure 1*, patients were divided into risk groups based on CHADS2 score and AF status. Every month, all living patients could experience AF, thromboembolic events,

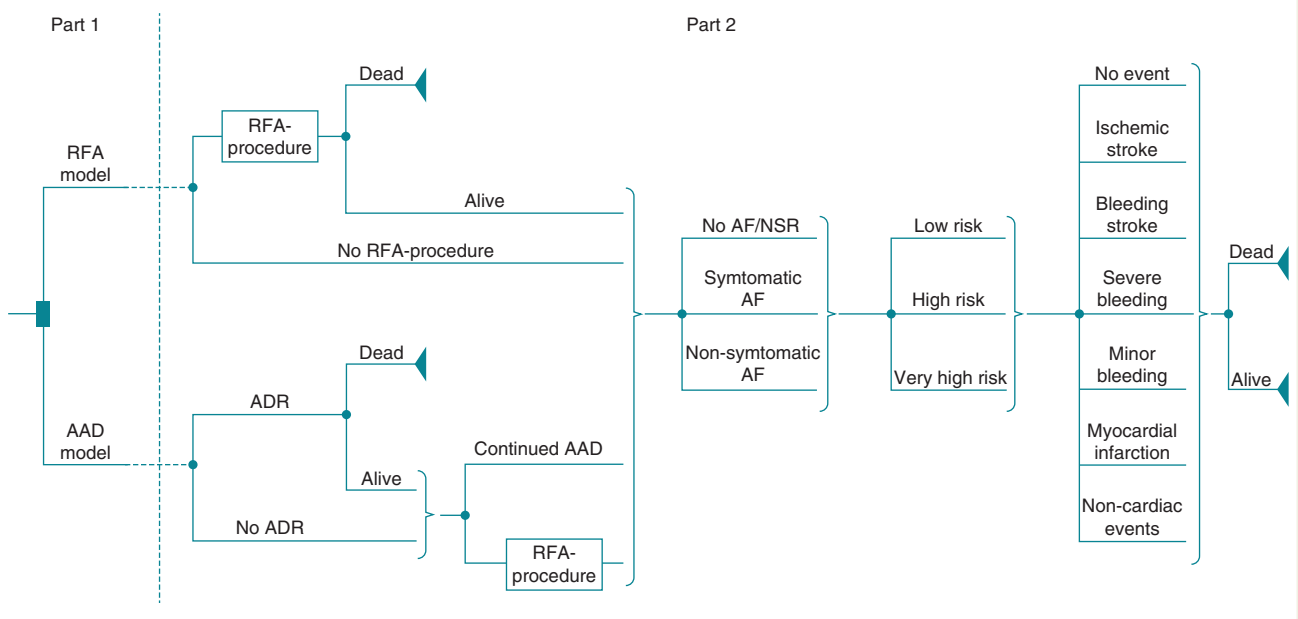

Figure 1 Structure of the decision-analytic Markov model. The treatment options are shown in *Part 1* of *Figure 1*. *Part 2* of *Figure 1* describes how patients could experience AF, thromboembolic events, bleeding, toxicity, and death (from cardiac and non-cardiac causes). Patients treated with AADs could do crossovers to RFA treatment and patients randomized to RFA could receive AAD treatment. The blocks named *RFA procedure* include a simple procedural model in which every RFA intervention could be repeated up to three times (Supplementary material). Based on the decision tree, clinical effects such as life years, QALYs, and costs were estimated. NSR, normal sinus rhythm; ADR, adverse drug reaction.

myocardial infarction, bleeding, drug toxicity, and non-cardiac events. Dependent on AF status, they could also do additional ablations or cross-overs to RFA treatment (*Table 1*, Supplementary material).

Statistical approach

Our current study analysed the MANTRA-PAF data using the methods presented in the MANTRA-PAF study plan.[17] The AF burden was investigated using the Mann–Whitney U-test, and freedom from AF was tested with Pearson's χ^2 test. If Holter data were missing, earlier data ($\geq$3 months) were used. Later on baseline data were used (in that order) when no earlier data were available.[17] The resource usage was compared using Student's unpaired *t*-test.

The symptomatic AF decrement was calculated using a *t*-test by comparing the EuroQol five-dimension (EQ-5D) data of those experiencing symptomatic AF at baseline but not at 12 months.

All analyses were performed with the use of SPSS 20 Windows (SPSS, Inc.).

Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation

The primary result of the MANTRA-PAF study[16] showed no significant difference between the groups in terms of total cumulative AF burden. However, significantly more patients in the RFA group were free from any type of AF at 24 months (124 out of 146 compared with 105 out of 148, $P = 0.004$). In the study, 54 patients (36%) randomized to AAD made a crossover during the first 24 months. The MANTRA-PAF study is described in detail elsewhere.[16]

Probabilities

In the model, patients were expected over time to relapse into AF, have additional ablations, or be treated with AAD. The long-term (>2 years) recurrence rate in RFA patients was calculated based on a meta-analysis of studies with a time horizon $\geq$5 years.[21–26] The long-term rate for AAD patients was estimated with a non-linear model based on Pappone *et al.*[20] Crossovers were expected, as patients could change treatment if the first strategy was not effective or due to its side effects. This was applicable especially to AAD patients, as they possessed a higher recurrence rate than patients treated with RFA.[20,29] The crossover rate during the first 24 months was obtained from the MANRA-PAF trial. The long-term crossover rate was calculated with respect to the AF recurrence in AAD patients (Supplementary material). In the baseline scenario, we also assumed that the significant difference in AF and symptomatic AF after 24 months should be taken into account in the remainder of the model. The risk of complications from the RFA procedure was obtained from the MANTRA-PAF trial.[16]

The model included the risk of AF-induced embolic events for both treatment groups. Besides usage of anticoagulants, the risk of events was expected to be dependent on age, gender, previous strokes, AF, diabetes, and high blood pressure; therefore, $CHADS_2$ index was used as a parameter.[2,19] All patients treated with warfarin at 24 months were expected to be treated with oral anticoagulation for the rest of their lives, regardless of the AF status.

Utility weights

The quality-adjusted life year (QALY) weights in the model during the first 24 months were obtained from the MANTRA-PAF study. EQ-5D data were collected before randomization and at the 12- and 24-month follow-up visits in the study and were translated into QALY weights using the British value-set published by Dolan.[30] The QALY weights at 24 months in MANTRA-PAF, adjusted for age as the individuals became older, were used in the long-term model.[16,31] Symptomatic AF and stroke were expected to decrease the quality of life of the individuals.[28] The quality of life and utility decrements used in the model are presented in *Table 1*.

Resource usage

Resources used in the ablation procedure include staff time, medications, anaesthesia, radiology, hospital care, sampling, lab tests, cardioversion, and catheters.

Both treatment groups' usage of pharmaceuticals, primary and hospital care resources was obtained from the MANTRA-PAF trial. This included the use of electrocardiogram, transthoracic echocardiogram, transesophageal echocardiogram, X-ray, exercise stress test, Holter monitoring, magnetic resonance imaging, computed tomography, cardioversions, ablations, and health care visits (*Table 1*).

Unit costs

Costs incurred for interventions and investigations in hospital or primary health care were provided by Linkoping University Hospital and the Southeast Healthcare region of Sweden. The monthly drug costs were gathered from FASS (Pharmaceutical Specialties in Sweden, www.fass.se). Unit costs are presented in *Table 1*.

Three percent discount rate was used in the base-case scenario for both costs and effects. All unit costs were adjusted to the price levels of the year 2012 and converted to euro using the exchange rate of 12 December 2012 (€1 = 8.7 SEK).

Results

Costs during trial follow-up

The 24-month average cost of treating PAF with first-line AAD was approximately half of the treatment cost using RFA. The intervention cost was mainly driven by RFA procedures and cardioversions. Patients treated with AAD had more physician visits (OR 1.43, CI 1.07–1.91). Resource usage during the first 24 months is presented in *Table 2*.

Model results in a lifelong perspective

The lifelong model analysis showed that RFA as first-line treatment implied a gain of 0.06 QALYs and an incremental cost of €3033, resulting in €50 570/QALY. *Figure 2* visualizes the outcome of the probabilistic model when the statistical validity has been tested 1000 times. The observations were spread into all four quadrants, indicating great uncertainty.

Significance of age

The cost analysis of MANTRA-PAF, presented in *Table 3*, shows the comparison between younger ($\leq$50 years) and older patients (>50 years). The significantly higher incidence of hospital visits in older patients treated with RFA was primarily due to AF (84.3%). There was a trend towards fewer ablation procedures in younger patients ($\leq$50 years) compared with older patients (>50 years) randomized to RFA (1.45 vs. 1.64, $P = 0.194$).

MANTRA-PAF data of patients $\leq$50 years for the first 24 months showed a significantly lower total cumulative AF burden (Mann–Whitney mean rank 48 vs. 31, $P < 0.001$, two-tailed) when RFA

Table 1 Summary of important numeric values and parameters

Variable	Probability %	Ref.
Experiencing AF at 24 months (AAD)	29	16
Experiencing AF at 24 months (RFA)	15	16
Stroke risk AF patients	According to $CHADS_2$ (Supplementary Material)	19
Hazard ratio stroke NSR	0.63	2
Crossover first 24 months		
All	36	16
≤50 years	51	[a]
>50 years	31	[a]
Reversion rate per month >24 months		
AAD	$0.25e^{-0.23t} + 0.75e^{-0.02t}$	20
RFA	0.8	21–26
Complications		
Complications of RFA procedure	11	[a]
Procedure-related mortality	0.14	[a]
ADR per months >24 months years	0.76	[a]
Fatal ADR (Class 1c) per months >24 months	0.027	13
Cost items	Unit cost (€)	
RFA procedure	10 033	[b]
Materials	4813	[c]
Day in hospital care	518	[b]
Stroke year 1		
Ischaemic	19 167	27
Bleeding	19 225	27
Stroke year >1	7028	27
Cardioversion	687	[b]
Electrocardiography	27	[c]
Transthoracic echocardiogram	301	[c]
Transesophageal echocardiogram	409	[c]
X-Ray	56	[c]
Holter monitoring	275	[c]
Computed tomography	290	[c]
Pharmaceuticals	Unit cost €/mg	
Warfarin	0.0460	[d]
Amiodarone	0.00195	[d]
Flecainide	0.00460	[d]
Propafenone	0.00253	[d]
Sotalol	0.00172	[d]
QALY weights		
AAD patients 24 months	0.86	[a]
RFA patients 24 months	0.90	[a]
Decrement for ischaemic stroke	0.15	28
Decrement for haemorrhagic stroke	0.30	28
Decrement symptomatic AF	0.13	[a]

AAD, anti-arrhythmic drugs; RFA, radiofrequency catheter ablation; AF, atrial fibrillation; NSR, normal sinus rhythm; ADR, adverse drug reaction.
[a]Previously unpublished MANTRA-PAF data.
[b]Unit costs obtained from report *Priser och ersättningar för Sydöstra sjukvårdsregionen 2012* [Pricing and payment for healthcare in the Southeast region of Sweden 2012].
[c]Cost data from the Department of Cardiology, Linköping University Hospital, Sweden, 2012.
[d]Prices obtained from Pharmaceutical Industry Association, www.FASS.se, accessed 26 October 2012.

was used as first-line therapy. A significant difference was not seen in patients >50 years (Mann–Whitney mean rank 107 vs. 108, $P = 0.894$, two-tailed). The differences in younger patients were even more notable as over 50% of the patients in the AAD group transferred to RFA treatment during the first 24 months. The proportion of patients free from AF is shown in *Figure 3*.

Table 2 Average consumption of health care resources in the MANTRA-PAF trial first 24 months

	RFA first (€)	AAD first (€)	Difference %	Significance (two-tailed)
Hospital visits	2373 (1802–2944)	1810 (1249–2371)	+31%	0.17
Investigation	1219 (995–1443)	1283 (1027–1539)	−5%	0.71
Intervention	16 394 (15 127–17 661)	6407 (4915–7899)	+156%	<0.01
Drugs	268 (213–323)	692 (600–784)	−62%	<0.01
Total	20 235 (18 674–21 947)	10 218 (8239–12 196)	+98%	<0.01

Confidence intervals are presented in parentheses. AAD, anti-arrhythmic drugs; RFA, radiofrequency catheter ablation.

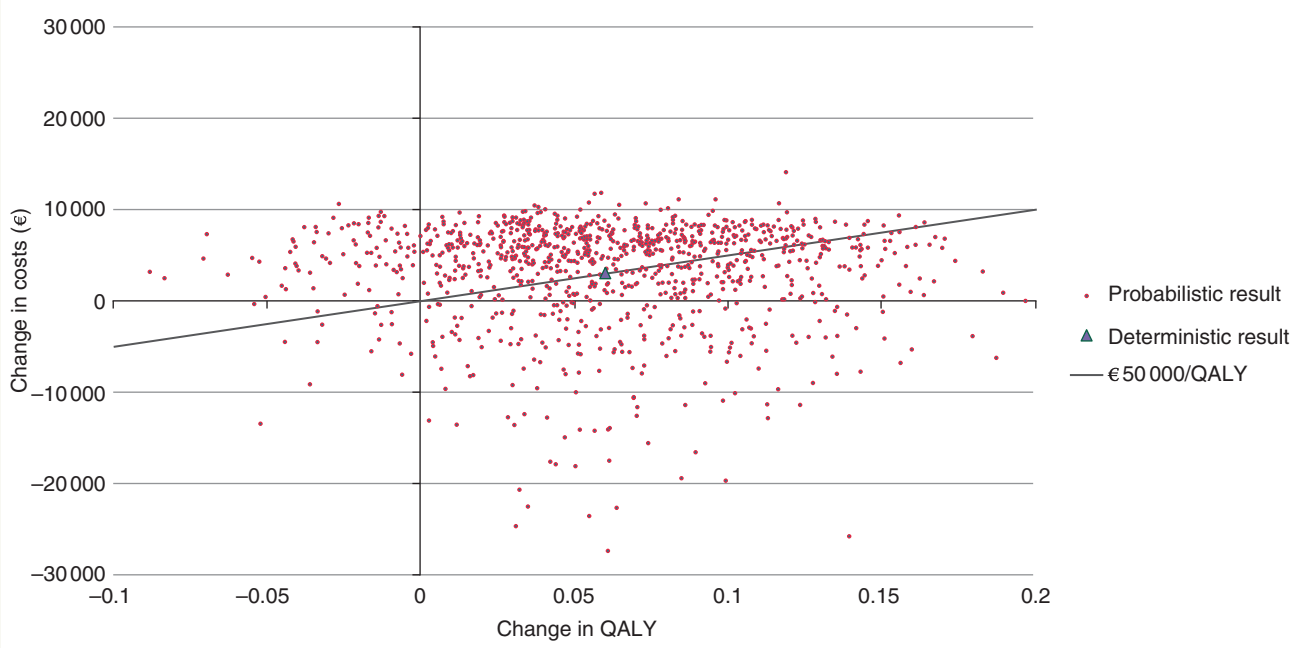

Figure 2 Probabilistic result based on Monte-Carlo simulation. The scatter plot shows the probabilistic result of the model when the statistical uncertainty of all parameters is tested 1000 times. The deterministic result is shown by the triangle.

Impact of age in a lifelong perspective

The lifelong model analysis when divided into age groups showed that younger patients gained an average 0.142 QALYs to an additional cost of €488 when treated with first-line RFA, resulting in an incremental cost-effectiveness ratio (ICER) of €3434/QALY (*Table 4*). In >50-year-old patients, the clinical effects of first-line RFA were lower (0.035 QALYs gained) and the costs were higher (€3685), implying an ICER of €108 937/QALY.

The probabilistic results were consistent with the deterministic result. With a confidence of ∼90%, the cost-effectiveness ratio of treating individuals ≤50 years of age with RFA as first-line therapy was <€50 000 per QALY. However, the willingness to pay for a QALY has to be very high (>€100 000) to make RFA treatment a cost-effective first-line strategy in older patients (Supplementary material).

Sensitivity analysis

A sensitivity analysis was performed to study the uncertainty of the long-term model parameters. *Table 4* shows the most important analyses divided into age groups. Both groups were sensitive to the readiness of offering crossovers and changes in the cost of RFA. Parameter values of recurrence and discount rates were important in older patients. The model was not sensitive to changes in QALY weights, utility decrements, other unit costs, or the stroke risk in patients free from PAF due to RFA. Furthermore, the sensitivity analysis of the cut-off age is shown in *Figure 4*.

Discussion

Our current substudy was the first attempt to determine the cost-effectiveness of RFA as the first-line treatment strategy in patients with PAF. Our analysis did not compare the effectiveness and cost-effectiveness of RFA and AAD as treatments exclusive of each other, the substudy instead investigated in what order they should be offered.

Our results showed that AAD should be offered as first-line therapy in the overall population. However, our subgroup analysis

Table 3 Consumption of health care resources in the MANTRA-PAF trial first 24 months divided into age groups (€)

Age	≤50		>50	
Treatment	**RFA first**	**AAD first**	**RFA first**	**AAD first**
Hospital visits	1541 (870–2213)	1589 (911–2267)	2630 (1914–3346)	1902 (1154–2651)
Investigation	622 (382–862)	1012 (673–1351)	1403 (1127–1680)	1398 (1062–1733)
Intervention	15 361 (12 309–18 412)	8201 (5432–10 970)	16 713 (15 323–18 102)	5659 (3878–7439)
Drugs	178 (108–248)	601 (488–714)	296 (223–359)	730 (597–833)
Total	17 782 (14 115–21 458)	11 484 (8017–14 952)	21 042 (19 213–22 870)	9689 (7257–12 120)

Confidence intervals presented in parentheses. AAD, anti-arrhythmic drugs; RFA, radiofrequency catheter ablation.

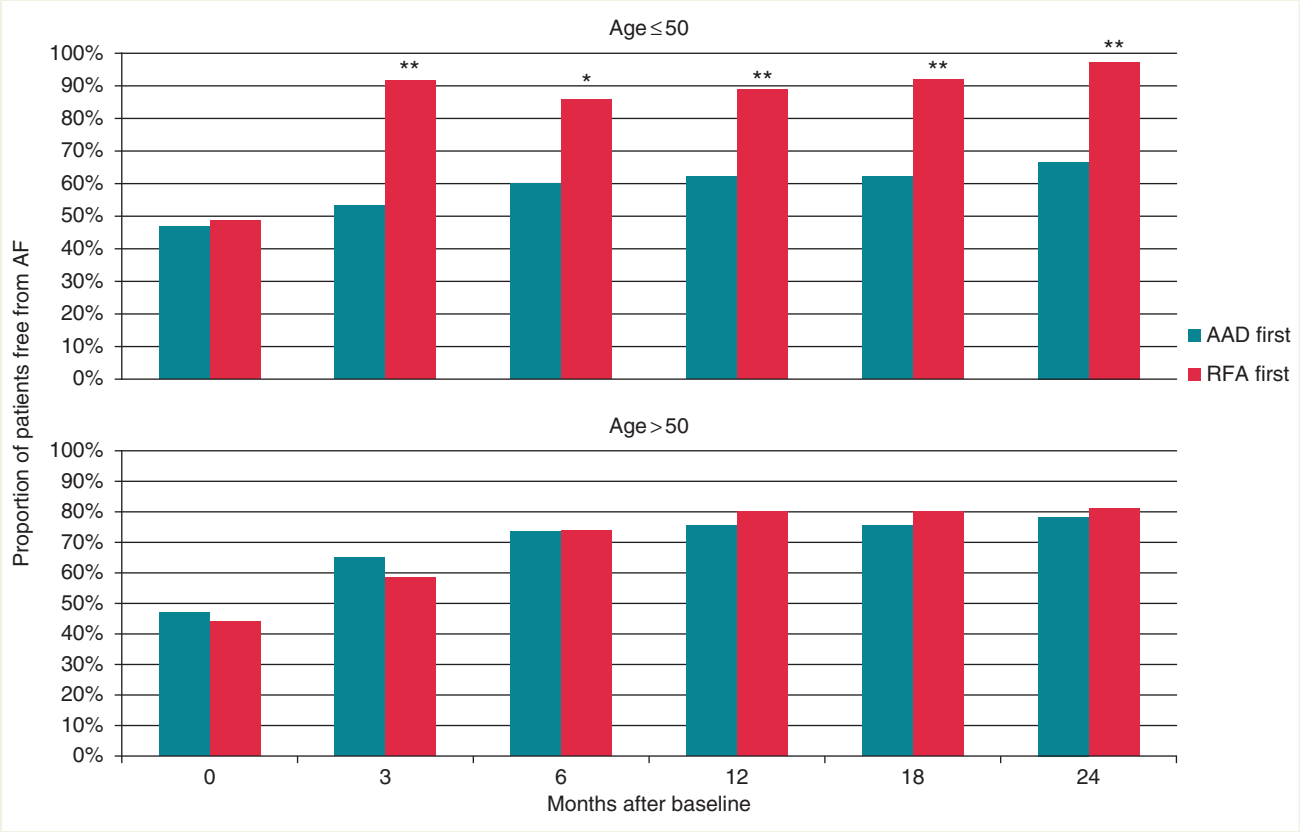

Figure 3 Proportion of patients free from AF. Bars indicate the proportion of the patients free from AF. Patients ≤50 years are shown in the upper part of figure and patients >50 years are shown in the lower part of the figure. *$P < 0.05$ and **$P < 0.01$.

showed that young individuals (≤50 years) were cost-effectively treated with RFA as first-line treatment. The high clinical efficiency of RFA and the fact that a large proportion was expected to be treated with RFA later were important contributing factors. The high efficiency of RFA could be because younger patients may be more likely to have earlier stages of AF, where the arrhythmia depends on focal firing rather than atrial fibrosis, and therefore, may have better results with catheter ablation. This area needs further investigation, but our findings indicate that younger patients (≤50 years) are more likely to experience symptoms and be exposed to an increased risk while being treated with AAD, to minimal, if any, cost savings.

The cut-off age (50 years) used in this study should not be considered as a recommendation for when to use RFA as the first-line strategy, treatment decisions still have to be made on an individual basis. The analysis of age significance indicated that first-line RFA could be offered to younger patients with PAF, but our clinical study was not designed to determine a specific cut-off age. Even if the analysis of age subgroups was not predefined in the MANTRA-PAF study protocol, it was selected as the main subgroup analysis performed in the economic evaluation as it is well known that young patients are difficult to treat with AADs.[18]

The reason why younger patients are difficult to treat with AAD could be that these patients, who are active, working and with a

Table 4 Sensitivity analysis: impact of important parameters

Scenario	Incremental cost (€)	Incremental QALY	ICER
≤50-year-old patients			
Crossover not allowed after 24 months	3903	0.863	4525
Discount rate 0%	−1392	0.177	Dominant
Discount rate 6%	1732	0.120	14 376
Time horizon 10 years	1351	0.113	11 958
No difference in AF between the groups after			
2 years	729	0.062	11 790
5 years	634	0.093	6856
The difference decreases as the patients do crossovers (base-case scenario)	488	0.142	3434
>50-year-old patients			
Crossover not allowed after 24 months	11 268	0.385	29 282
Discount rate 0%	2241	0.039	57 734
Discount rate 6%	4889	0.031	157 237
Time horizon 10 years	4622	0.031	149 132
No difference in AF between the groups after			
2 years	3724	0.019	200 757
5 years	3704	0.027	138 901
The difference decreases as the patients do crossovers (base-case scenario)	3685	0.035	108 937

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; AF, atrial fibrillation.

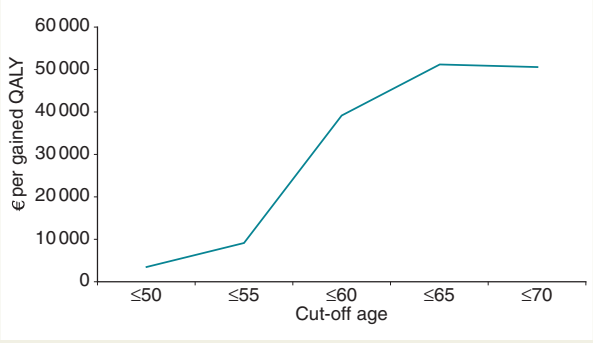

Figure 4 Significance of cut-off age. The curve shows how the incremental cost-effectiveness ratio for younger patients is dependent on the cut-off age.

low risk of thromboembolism without indication for anticoagulation, may be less willing to accept antiarrhythmic medication twice a day if one catheter intervention is as or more effective for reduction or elimination of their symptoms.

In comparison with a 24-month cost analysis[32] of the RAAFT study,[14] the cost of RFA in this study was significantly higher (€20 235 vs. €11 707), while the cost of the AAD treatment was slightly lower (€10 218 vs. €11 009), which could be explained by the cost of the ablation procedure and differences in the crossover rates.

There is a possibility that the crossover rate is lower in general clinical practice than in the study, even though the participating centres were advised to be conservative with RFA treatment.[17] The techniques for catheter ablation have also improved since the MANTRA-PAF trial was conducted, and the results of contemporary RFA treatment may therefore be superior to what was found in the trial.

Lifelong models based on short-term data always include an uncertainty about the long-term effects. We have tried to minimize this uncertainty by testing the sensitivity of the lifelong estimates with both deterministic and probabilistic methods.

When analysing MANTRA-PAF data, crossovers and clouding effects of these must be taken into account. In the trial, RFA and AAD had almost the same clinical effectiveness as first-line treatment. However, as shown in the sensitivity analysis, it is important to apply RFA when AAD fails; otherwise, RFA would probably become the superior treatment.

Conclusion

Radiofrequency catheter ablation as first-line treatment is a cost-effective strategy for younger patients with PAF. However, the cost-effectiveness of using RFA as first-line therapy in older patients is uncertain, and in most of these cases AAD therapy should be attempted before RFA.

Supplementary material

Supplementary material is available at *Europace* online.

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