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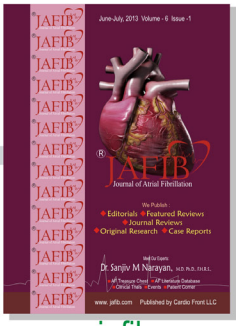

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Cost-Effectiveness of Atrial Fibrillation Ablation

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Abstract

Atrial fibrillation (AF) is a frequently encountered rhythm disorder, characterized by high recurrence rate, frequent hospitalizations, reduced quality-of-life and increased the risk of mortality, heart failure and stroke. Along with these clinical complications this type of arrhythmia is the major driver of health-related expenditures. Radiofrequency catheter ablation (RFA) of atrial fibrillation has been shown to improve freedom from arrhythmia survival, reduce re-hospitalization rate and provide better quality-of-life as compared with rate control and rhythm control with antiarrhythmic therapy. Efficacy of AF ablation in terms of outcomes and costs has an evolving importance.

In this review, we aimed to highlight current knowledge on AF ablation clinical outcomes based on results of randomized clinical trials and community-based studies, and overview how this improvement in clinical end-points affects costs for arrhythmia care and cost-effectiveness of AF ablation.

Introduction

Atrial fibrillation (AF) is the most frequently encountered arrhythmia,characterized by high recurrence rate, frequent hospitalizations, reduced quality-of-life (QoL) and increased the risk of mortality, heart failure and stroke.[1,2] Along with these clinical complications AF is the major driver of health-related expenditures: its economic burden was estimated to be $6 -26 billion in US and €13.5 billion in EU.[3-6] AF might also exacerbate the clinical course and prognosis of underlying disease[7-9] and consequently increase costs for its care.[9,10]

The current standards of AF management include several strategies which might differ according to the type of AF and patient-specific characteristics: rate-control (RateC), including medical therapy or ablation of atrioventricular node with pacemaker implantation, and rhythm control (RhyC) with either antiarrhythmic drugs (AADs), electrical cardioversion, with further long-term AADs treatment for rhythm maintenance, or radiofrequency catheter ablation (RFA). All these strategies might include preventive therapy with antithrombotics according to the patient`s risk of stroke.

Evidence, based on results of randomized controlled trials (RCTs), suggests no differences between RateC and RhyC with AADs or electrical cardioversion in terms of major adverse outcomes, like mortality, risk of stroke and heart failure for patients with persistent/paroxysmal AF.[11-17] RhyC is not an appropriate management strategy for elderly patients with major comorbidities,[12,15] because of increased risk of death. On other hand, RhyC is associated with symptoms improvement, better QoL, higher exercise tolerance, and improvement of left ventricular function and its benefits might be more pronounced in younger patients and those with paroxysmal AF.[18-21]

Real-time observations of AF management in unselected patients, presented in the community-based survey RECORDAF, demonstrated that RhyC was associated with 1.34 times (95%CI 1.15-1.55, p=0.0002) higher likelihood of therapeutic success than RateC strategy, reducing probability of paroxysmal AF progression to permanent one by 80% (OR-0.20, 95% 0.17-0.25, p<0.0001).[22]

However, it is necessary to emphasize major limitations of RhyC strategy as the adverse effects of AADs and frequent hospitalizations due to arrhythmia recurrence.[15-21]

Ablation of AF is a potentially curative approach in arrhythmia treatment, characterized by higher rate of normal sinus rhythm (NSR) and better of QoL, less hospitalization rate and less drug-toxicity related complications as compared to conventional medical therapy.[23-30]

The goal of this review is to highlight the current knowledge on cost-effectiveness of AF ablation.

Overview of AF Ablation Studies

Several clinical trials demonstrated RFA as an effective procedure in modification of clinical outcomes in patients with AF as compared to RhyC with AADs strategy.[23-30]

Key Words:
Atrial fibrillation, radiofrequency catheter ablation, cost-effectiveness analysis

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RFA in patients with chronic or paroxysmal AF resistant to anti-arrhythmic drugs was found to be superior to RhyC with AADs in terms of maintenance of sinus rhythm 1 year after procedure; 74-89% of patients who underwent RFA and only 16-58% of patients on AADs therapy were in NSR.[23-27] Among patients with symptomatic paroxysmal AF who underwent ablation as the first therapy of choice, 85-87% of patients were free from arrhythmia at the end of 1-2 years of follow-up.[28-30] Patients underwent RFA had reduction of symptoms severity related to arrhythmia by 76%, greater improvement in QoL and exercise tolerance as compared to those on RhyC with AADs.[24,27-29] It is worth mentioning, that number of hospitalizations was significantly less in group of patients undergoing ablation as compared to those on AADs therapy. The latter strategy was accompanied by adverse effects related to AADs in 8-23.3% patients.[26,27,29]

Despite invasive nature and higher initial cost of ablation, it is an attractive approach in cure of AF because of its association with higher NSR rates during follow-up, better indexes of QoL, larger reduction in symptoms severity, less rate of re-hospitalizations and adverse effects of AADs.

The current guidelines-based[5,6,31] indications are as following: RFA is indicated in subgroup of patients with symptomatic drug-resistant paroxysmal AF (level of evidence/class IA), and it might be a reasonable choice of therapy for patients with paroxysmal AF as the first line of therapy (level of evidence/class 2A); it might be considered for patients with persistent AF resistant to drugs (level of evidence/class 2A), and as the first line of therapy for patients with persistent AF(level of evidence/class 2B), though evidence is not yet sufficient for the latter subgroup and is based on expert opinion.

Recent AFAPS survey [32, 33] on outcomes of RFA in 10 European countries (Belgium, France, Germany, Netherlands, Greece, Italy, Spain, Denmark, Chech Republic and Poland, centers with >50 procedures/year) demonstrated that freedom from arrhythmia rates were close to those reported in RCTs. This survey included 1391 patients with paroxysmal/ persistent AF who underwent RFA. About 70% of patients had paroxysmal AF, 28% - persistent and the rest of patients had permanent AF; 60% of patients had underlying structural heart disease. The indications were symptoms in 89% and improvement in QoL -74%. About 91.4% of patients were discharged in NSR after 3 days of hospitalizations. RFA related procedural complications occurred in 7.7% of patients, including 1 death. One-year outcomes data for this survey were presented at ESC congress in 2012 – of 1391 patients 6.5% were lost to follow-up and outcomes of 1300 patients were as following: 88.1% of patients were in sinus rhythm, re-admission rate was 30% including 21% for recurrent AF and repeated RFA was applied to 18% of patients.[33] Number of patients without symptoms increased from 13.1% to 55%. Adverse effects of RFA reduced to 2.6%. It is worth highlighting that about 13% of patients included in this survey were asymptomatic and the choice of RFA therapy was based on patients` willingness to improve QoL, to have a drug-free lifestyle and to maintain the NSR.

Thus, RFA is an effective approach in the treatment of paroxysmal/ persistent AF resistant to drug therapy and as a first line of therapy in symptomatic paroxysmal AF with clear advantages in sustaining NSR, improvement of quality of life, reducing re-hospitalizations and improvement of symptoms. The results of community- based studies are comparable to those of RCTs, if performed in centers with certain volume of procedures. The main disadvantage of the procedure is invasive nature and certain percentage of peri-procedural complications.

AF Ablation and Costs

Total costs for AF care are constituted in major part by costs for hospitalizations, in-hospital procedures and expenditures for treatment of complications.[3] In a study of expenditures for AF care in US, cost for hospitalization constituted 44% of general cost, followed by treatment of complications and other expenditures.[3] In Netherlands total annual cost of AF (prevalence 5.5%) care for 250.470 patients over 55 years old was reported to be as high as €583 million; the costs increased with age of the patients and treatment of complications like stroke.[34] The analysis of AF care costs in Germany[35] showed that majority of patients received RateC therapy-58% and 27% received RhyC with AAD. The average annual cost for AF care was equal to €827 per patient; of which 44% was due to re-hospitalizations and 20% - AADs. The annual cost for RhyC was as twice higher than for RateC (€1572 per patient vs €780 per patient). Overall annual cost for 800.000 patients with AF was equal to €660 million.

As mentioned above ablation of AF is associated with better outcomes, especially in terms of major driver of cost like re-hospitalization rate; however equipment, catheters, navigation systems, peri-procedural care and physician expenses are the factors that increase the initial cost of procedure which might be higher as compared to AADs strategy initial costs.

The costs for AF ablation in European countries, according to administrative data analyses and surveys vary between €8868 and €9600 per patient,[36,37] being higher for AF with structural heart disease.[38] However, hospital care costs tend to reduce significantly after procedure as compared with pre-ablation period. Comparative analysis of healthcare expenditures in US [39] 6 months before and 3 years after RFA in 3194 patients demonstrated significant reduction in number of hospitalizations; emergency department, in-hospital and out-hospital visits after ablation, saving expenses for hospital care by $3200-$9600 per patient.

Cost-comparative studies[40-44] analyzed the costs for RFA in comparison with RhyC and RateC in time-dependent manner accounting for the freedom from arrhythmia, re-hospitalizations and complications rates. Specifically, the analyses include the timing of costs equalization in long-term perspective when beneficial clinical outcomes might translate into saving or reduction of costs.

As we previously summarized[45] the initial costs of AF ablation varied between €1590-4715 per patient, $10465-18151 per patient and ¥1063200-4041289 per patient depending on the type of AF and complexity of procedures, exceeding the initial costs for RhyC with AADs by three times. However, during follow-up, the annual spending per patient after RFA was significantly lower than for AAD therapy (€634 vs €2263, 40 €448 vs €1590 ,41 $1597-2132 vs $4840-44 $2358 vs 349743). As a result at the end-of follow-up the total costs for RFA and RhyC with AADs strategies equalized or become even smaller than for comparative strategy. The cross-over time points, when the costs for two strategies equalized showed difference according to the type of AF and indication for RFA, complexity and need for repeat procedures. The earliest equalization of costs at the second year was reported for RFA used as a first line of therapy in

patients with paroxysmal AF,[43] while for patients with paroxysmal/ persistent AF resistant to drug therapy and single ablation procedure the equalization occurred at 3-5 years, in cases of repeat and complex procedures it extended up to 9-14.3 years.[40-42, 44]

Though these studies were performed in different countries with diverse costs for medical care, the dynamics of cost measures show similar pattern. Despite the higher initial cost of RFA as compared to drug treatment, in long-term perspective the total costs of RFA become less than total costs for drug therapy. This advantage is more prominent in group of young patients with paroxysmal AF undergoing RFA as the first line of therapy or patients with paroxysmal AF without need for repeat and complex procedures. In contrary, the drug-therapy cost remained unchanged because of high arrhythmia relapse rate requiring re-hospitalizations and in-hospital procedures.

AF Ablation and Cost-Effectiveness

Cost –effectiveness of any ``new`` intervention is assessed in comparison with so called ``old`` intervention with purpose to define whether each gain in clinical outcome lies within acceptable increments in costs to be paid and is measured as the incremental cost-effectiveness ratio (ICER) .[44,45] QAly– quality adjusted life years - is a measure of the number of healthy years lived gained as a result of intervention. In other words the cost-effectiveness of AF ablation vs medical therapy is the gains of RFA in terms of better outcome and the costs required to cover expenses to achieve this additional benefit. The intervention is accepted as effective only with achievement of desired clinical outcomes at acceptable threshold values.

There are two types of cost-effectiveness studies: based on clinical trial data and decision-analytical models. Few decision-modeling studies [48-50] evaluated whether RFA would be cost-effective in special subsets of patients with arrhythmia based on the data of RCTs, controlled prospective studies, registry and survey data, as well economic data based on healthcare and insurance expenditures (Table 1).

It has been found that RFA might be cost-effective as compared to reference RateC strategy in elderly patients with AF at moderate risk of stroke, if the risk of stroke would be reduced sufficiently.

Chan et al.[48] demonstrated that RFA might be a cost-effective strategy in patients with AF of 55 -year- old and 65- year- old at a moderate risk of stroke as compared to RateC strategy. In their decision model authors assumed that RFA success would be equal to 80% at the first year and AF would relapse in 2% of patients, while only 38% of patients in the RateC would achieve therapeutic success. The stroke, assumed to occur in 1.3 and 0.7% of patients of 65 and 55 years of age at moderate risk of stroke receiving warfarin therapy. Analysis showed that lifetime costs per patient vary being the highest for RFA ($52369 and $59380 for patients of 65 years and 55 years) and the lowest for RateC ($39391and $50509, respectively), and RhyC with AADs in between ($43358 and $55795 respectively). The costs for 55- year- old also would be higher as compared to elderly because of longer life expectancy. Authors established that AF ablation is effective in reduction of unfavorable outcomes at the cost within accepted threshold limits ($50000 to $100000) only in elderly patients at moderate risk of stroke as compared to RateC strategy (ICER $51800/QALy and $28700/QALy for 65 - and 55-year-old, respectively). RhyC with amiodarone was shown to be ineffective in terms of costs and outcomes as compared with RateC, the latter one was selected as a reference strategy. Patients undergoing RFA would have higher QALy rates as compared with RateC and RhyC AAD treatment arms, which mean they would have gain more years free of unfavorable outcomes (11.55 vs 10.81 and 10.75, respectively). The sensitivity analysis conducted with the aim to define the variables which might increase the costs above acceptable values demonstrated that all variables` costs were within threshold limits. The threshold analysis of ICER values demonstrated that the AF ablation would be cost effective only when the risk of stroke is reduced by 42% in 65 –year-old and 11% in 55-year-old groups. The strategies in the subgroups of patients with low risk of stroke were not cost-effective.

In another analysis from UK, [49] RFA was shown to be cost- effective for AF patients resistant to RhyC with AADs irrespectively of CHADS score and risk of stroke if their life-long QoL measure will be equal to those of general UK population.

McKenna et al.[49] in their decision- model study made assumptions for patients of average age of 52 years (80% of male gender) with paroxysmal AF with and without risk of stroke ($CHADS_2$ score varied between 0 and 3) undergoing either ablation after at least one unsuccessful attempt of treatment by AADs or long-term RhyC AADs therapy. The success rate at first year was assumed to be 84% for ablation and 38.6% for AAD arms, consequently the recurrence rate for AF was accepted as 3.35 and 28.8%, respectively for each group. The short-term outcomes included the freedom from arrhythmia, procedural complications and complications related to drug toxicity; long-term outcomes include NSR, stroke, mortality and AF recurrence rate. The outcome measure was QoL in presence of NSR, with assumption that strategy would be cost-effective if the patients achieve the quality-of-life standards for general UK population. The costs for treatment were retrieved from UK NHS database and personal social services. Analysis was performed for 5-year and life-long effects. Cost analysis demonstrated the higher life-long per patient values for ablation (for CHADS 0-3 - £25240-£28343) than for medical therapy (£14415-£18107). The cost-effectiveness threshold was accepted at £20000-£30000. The ablation strategy was found to be cost-effective only for life-long outcomes and costs. The patients in ablation arm would gain more QALy (for CHADS 0-3 – QALY 12.37 -11.49) as compared to AADs arm (10.98 -10.19). This gain in QALy would require additional spending (ICER for CHADS 0-3 - £7763-£7910) within acceptable threshold of £20000-£30000. The probability for ablation strategy being cost-effective was 98.1-100%. The sensitivity analysis showed that following scenarios might increase the costs above the threshold value: increase in annual relapse of AF >15%, absence of difference in outcome measures between ablation and medical therapy, and prognostic significance of NSR.

AF ablation plus antiarrhythmic drug therapy was also shown to be cost-effective in another AF population: average 60 years old male patients with symptomatic paroxysmal AF resistant to 1 or more AAD, without history of stroke, heart failure or structural heart disease.[50]

In a study by Reynolds et al.[50] the assumption of AF relapse rate patients undergoing RFA were: 40% and 25% would have AF recurrence after 1st and 2nd years of procedure, while patients in AADs arm would have recurrence rate of 75% and 60%, respectively. Freedom from arrhythmia and QoL constituted outcome measures. Analyses were done for 5-year projection of costs. The 5-year

cumulative cost of AF ablation per patient was higher than for medical rhythm control ($26584 vs $19898). However, the mean QALy was higher for RFA as compared to AAD strategy (3.51 vs. 3.38), which was explained by increase in costs for AAD treatment due to higher AF recurrence rate and need for adjustments in treatment. The AF ablation was found to be cost-effective with ICER value of $51431/ QALy being within the acceptable threshold range. Sensitivity analysis demonstrated that time (short-term 3 years), cost ($20000) and low success rate of RFA, higher need for rate control were factors that might increase the incremental value over threshold of $100000.

Recently published health technology reports for different countries on economic evaluation of RFA cost-effectiveness reported similar results .[37,51,52]

There are no published prospective clinical trial based cost-effectiveness analyses of RFA vs RhyC with AADs/RateC. Currently ongoing CABANA trial [53] on the effects of RFA vs RhyC or RateC on mortality in untreated or incompletely treated patients with AF (patients >65 years old and <65years old with >1 risk factor for stroke) will assess also the costs, resource utilization and cost-effectiveness of the RFA intervention with follow-up up to 5 years.

It is also not known whether the newer generation of antiarrhythmic drugs might affect the cost-efficacy of AF ablation.

Conclusions:

Thus, current knowledge based on the RCTs and community-based studies suggests that AF ablation is associated with the higher freedom from arrhythmia rate, improvement of quality- of-life, reduction of symptom severity and re-hospitalization rate as compared with rate and medical rhythm control strategies.

These clinical gains of RFA might translate into benefits in costs for AF care as compared to reference strategies. Initial higher costs of RFA tend to reduce over the long-term follow-up and equalize with the medical rhythm control care costs, with the earlier cost equalization for younger patients, without comorbidities and less complex procedure.

Decision- analytical modeling studies allows suggesting successful AF ablation alone or with concomitant AADs therapy as cost-effective strategy in special subgroups of patients if desired clinical outcomes/ quality of life measures will sustain at long-term, risk of stroke will reduce in elderly patients and AF relapse rate and cost of procedure will not exceed pre-specified levels.

Results of ongoing prospective clinical trials based analyses should be awaited to confirm current knowledge and extend it if the benefit of RFA in mortality reduction will be demonstrated. Additional analysis of cost-efficacy in subgroups of patients with broader contemporary guideline indications for AF ablation needs to be addressed.

Table 1: Decision analytical studies on cost-effectiveness of AF ablation

Study	Study population	Cost	Years	QALy	ICER	Threshold value
McKenna et al.48	52y patients at different risk of stroke CHADS2 0-3	RFA £25240-£28343 AAD £14415-£18107	Life-long	RFA 12.37-1.49 AAD 10.98-10.19	£7763-7910	£20000-£30000
Reynolds et al.49	Paroxysmal AF refractory to 1 or more AADs No SHD, stroke, HF	RFA +AAD $26584 AAD $19898	5 years	RFA+AAD 3.51 AAD 3.38	$51431/ Qaly	$50000-$100000
Chan et al.50	55 y and 65 y patients at moderate risk of stroke	65 y R - $39391 AAD- $43358 RFA - $52369 55 y R-$50509 AAD - $55795 RFA - $59380	life-long	65 y 10.81 10.75 11.55 55y 13.95 13.81 14.26	65y reference domi-nated $51800/ QALy 55y reference domi-nated $28700/ QALy	$50000-$100000 Stroke reduction by 42% Stroke reduction by 11%

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