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Review Article

Cost of AF Ablation: Where Do We Stand?

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Atrial fibrillation (AF) is a common and frequently disabling chronic condition associated with significant patient morbidity and affecting an increasing stratum of our ageing society. Direct costs related to atrial fibrillation are comprised from direct cost of medical therapy, catheter ablation, and related hospitalizations and imaging procedures, with indirect costs related to complications of the primary therapeutic strategy, management of related conditions, as well as disability and loss in quality of life related to AF. Over the last decade, catheter ablation became a promising alternative to rate and rhythm control among symptomatic AF patients. The purpose of this paper is to describe the evidence on the financial implications related to ablation based on published data and authors' experience.

1. Implications of Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia [1]. It is responsible for most arrhythmia-related hospitalizations and leads to the greatest length of hospital stay associated with any disorder of the cardiac rhythm [2]. While associated with increased mortality in the affected patients, atrial fibrillation is thought to be responsible for the majority of thromboembolic events, many of these preventable [3]. Strokes reported with equal frequency in patients with both paroxysmal and permanent atrial fibrillation have been more devastating and associated with greater disability than embolic events related to other cardiac disorders [4–6]. Patients with AF account for 15% of all strokes and are at a significantly increased risk of death due to stroke and heart failure [7]. Of all patients experiencing a stroke related to AF, 60% will be discharged with a new disability while 20% will die [8]. While the most apparent negative outcome of this arrhythmia, strokes are by far just the tip of the iceberg. Patients with AF are prone to develop rapid poorly controlled heart rate associated with significant disability and development of cardiomyopathy in some patients. These patients along with those who have hypertrophic cardiomyopathy and other less obvious etiology of diastolic dysfunction are at substantial risk of developing congestive heart failure while in AF [9]. Recent evidence also suggests greater mortality simply related to faster heart rates in some patients [10]. A staggering 70%–80% of AF patients are admitted to hospital at some point in the course of their disease. Finally, AF is a source of disability for many younger members of the workforce who feel out of control when their heart rate suddenly becomes erratic. It may lead to frequent hospital visits [11], inpatient and outpatient monitoring, imaging and cardioversion procedures, and, of course, invasive therapies ranging from cardiac pacing in patients with concomitant dysfunction of the sinus node, to ablation of the AV node in concert with permanent pacing or cardiac resynchronization therapy and to the "curative" ablation of the cardiac tissues thought to trigger and perpetuate AF.

2. Sources of Cost in AF

Multiple negative health outcomes in AF patients as well as AF treatment strategies contribute to an ever-growing tap drawn on the healthcare system and the society at large. To make matters worse, AF is a disorder affecting preferentially older members of the society with greater than 10% prevalence in those over the age of eighty [4]. This is a disastrous proposition in an aging society with

exponentially increasing occurrence of this condition and subsequently skyrocketing costs related to the associated morbidity, disability, and treatment. A recent systematic review of the cost of AF care revealed that the overall average annual cost to support the system to manage one AF patient is $7,226 with a range of estimated costs as high as just over $10,000 [12]. While these costs are substantial, they represent only about one quarter of the entire health system costs for patients with AF. Two studies estimated the entire system cost for all care for patients with AF to range between $20,613 to $40,169. Hospitalizations are the most important determination of total cost (58%) with the cost of a single acute admission in Ontario with AF as a primary diagnosis of $24,096 [13]. Rhythm and rate control strategies targeting disability related to AF have seen little evolution over the years, and no radically new agents have come to market in decades. Multiple comparisons of these strategies have come in short of finding a winner, and both approaches have had significant clinical limitations [14–16].

3. Cost Containment Strategies

A number of studies have looked at the potential cost containment strategies. Of these, the most obvious is greater attention to anticoagulation therapy in patients suffering from AF. The bulk of current cost of AF care is related to thromboembolism, yet currently as few as 10%–20% of the AF patients are treated with appropriate prophylaxis strategies [5]. Those who do take oral anticoagulants spend much of their time taking subtherapeutic doses of the medication placing them at risk of stroke, while others take supertherapeutic doses and run a significant risk of bleeding given a very narrow therapeutic range of warfarin. Multiple new medications targeted to prevent stroke in AF patients are becoming available, but while easier to use, these may have their own risks related to lack of reversibility and may carry a substantial upfront cost [17]. A new antiarrhythmic medication, dronedarone, available to the clinicians in Canada for just over a year had shown promise of lesser risk of toxicity and uniquely was shown to reduce morbidity and mortality in AF patients, but has done so despite being no more effective at controlling the actual rhythm disorder than the other drugs. The impact this strategy will have on the cost of care in AF remains to be determined.

Another such strategy has to do with ablation. First promise for a potential cure for AF came in 1998 when it became apparent that ectopic atrial activity originating in the pulmonary veins may be responsible for initiation of AF and could be targeted with radiofrequency energy [18]. The field of targeting AF triggers had seen substantial progress since this discovery with multiple tools coming to market over the last decade in an effort to improve the safety and efficacy of these procedures. Most of these strategies involved delivering various types of energy just proximal to the insertion of the pulmonary veins into the left atrium using conventional, irrigated tip, and circular- and balloon-shaped catheters. Another strategy that was first described in 2004 and had seen much technological attention has been that of targeting tissues thought to perpetuate AF or presenting so-called AF substrate [19]. These latter efforts have focused on elimination of the viable atrial myocardium displaying particularly disorganized activity during AF or delivering energy over autonomic nerve ganglia thought to initiate and perpetuate the arrhythmia.

These approaches have shown promise in a multitude of individual center and multicenter randomized trials uniformly showing clinical benefit of ablation over antiarrhythmic drug therapy with respect to sinus rhythm maintenance, quality of life, and arrhythmia, related hospitalizations in at least some populations [20–22].

Unfortunately, in this rapidly evolving field most studies have focused on short-term comparisons between ablation and medical therapy as well as on the assessment of the relative efficacy of ablation strategies and tools. While the literature is unanimous in praising ablation as winner with respect to control of symptomatic arrhythmia over 6–12 months, until recently little has been published about the long-term efficacy of ablation and even less about its effect on mortality and embolism. Initial reports of AF ablation suggested greater than 90% freedom from arrhythmia among treated patients. Now a decade later many are publishing results suggesting much more modest upfront benefits with a difficult to ignore success attrition rate. While long term success rates varied drastically in these publications from 9% very late recurrence rate reported by Shah et al. [23] to 92% recurrence rate reported by Katritsis et al. [24], most investigators agreed that AF ablation does not impart cure of this condition in a significant number of patients. Incidentally, our findings of 42% recurrence following pulmonary vein antrum isolation with 30% likelihood of further arrhythmia in patients thought of as "cured" one year following the procedure represent a medium late recurrence rate compared to these publications, are in line with the recent report by Bertaglia et al. [25], and demonstrate a lower annual recurrence rate following the first year compared to the report by Tzou et al. [26]. Moreover, patients suffering from further AF are subjected to multiple repeat procedures further contributing to the growing cost to healthcare. Our well-characterized cohort of patients for the first time illustrated ever-diminishing return on this investment with 50% success of the second and 25% success of the third ablation.

4. Ablation versus Medical Therapy: Cost Perspective

Several projections of cost of care of an AF patient have been published in an attempt to estimate the relative cost of ablation and contrast it to the cost of medical therapy over time. A study directly comparing the costs of ablation and medical therapy in the Canadian healthcare environment has been published [27]. Costs related to medical therapy in the analysis included the cost of anticoagulation, rate and rhythm control medications, noninvasive testing, physician followup visits, and hospital admissions, as well as the cost of complications related to this management strategy. Costs related to catheter ablation were assumed to include

the cost of the ablation tools (electroanatomic mapping or intracardiac echocardiography-guided pulmonary vein ablation), hospital and physician billings, and costs related to periprocedural medical care and complications. Costs related to these various elements were obtained from the Canadian Registry of Atrial Fibrillation (CARAF), government-fee schedules, and published data. Sensitivity analyses looking at a range of initial success rates (50%–75%) and late attrition rates (1%–5%), prevalence of congestive heart failure (20%–60%) as well as discounting varying from 3% to 5% per year were performed. In this study, the cost of catheter ablation strategy ranged from ~US$14,000 to US$18,000. It was assumed that patients who required anticoagulation prior to ablation would continue on this therapy following the procedure with an annual average followup cost of US$1400 to US$1800 among the ablated patients. The annual cost of medical therapy ranged from US$3,600 to US$4300. The latter estimate was supported by the findings from the FRACTAL registry which prospectively collected clinical and cost data for 973 patients with atrial fibrillation [28]. The study projected costs of ongoing medical therapy and catheter ablation to equalize at 3.2 to 8.4 years of followup in this study but did not take into account development of the novel antiarrhythmic and thromboprophylactic strategies not available at the time of the publication.

A number of AF cost estimates have been published internationally. Treatment costs associated with followup of AF patients including hospital admissions, emergency room visits, and testing and followup with cardiologists, internists, and family physicians were analyzed in France [29]. This analysis stratified patients according to therapeutic strategy—rate or rhythm control—as well as according to concomitant congestive heart failure symptoms. The authors estimated the average total 5-year cost of AF at 16,539 Euro. In a study from Bordeaux, 118 patients 52 ± 18 years of age with symptomatic drug refractory paroxysmal AF underwent 1–4 pulmonary vein isolation procedures per patient [30]. All patients previously failed at least 2 antiarrhythmic drugs, with close to 80% having failed amiodarone. During a followup period of 32 ± 15 weeks, 72% of them were free of AF without the use of antiarrhythmic drugs. The cost of care was estimated in 2001 Euro. Procedural costs and costs related to hospitalization were obtained from hospital billing data. The cost of medical therapy was based on review of 20 consecutive patients and accounted for antiarrhythmic drugs used, frequency of symptoms prior to ablation, frequency of visits to the emergency room, doctor's office visits, and hospital admissions. All future costs were estimated using 5% discounting/year. It was assumed that patients were hospitalized for 5 days around the time of ablation. Neither complex mapping systems nor intracardiac echocardiography were used or accounted for. Furthermore, it was assumed that patients were treated with a fixed antiarrhythmic routine for 12 months prior to ablation. The projected annual cost of medical therapy was estimated at 1,590 Euros. The upfront cost of ablation was estimated at 4,715 Euros. Assuming that ablation was successful in 28% of all patients, the cost of ongoing care in the ablated patients was estimated at 445 Euros per year. As a result, the costs of medical therapy and ablation crossed over between four and five years. Since no complications occurred in the ablated patients in this study, these were not accounted for in the analysis. Furthermore, followup costs were accrued only for patients failing AF ablation with no additional cost assigned to followup of the successfully ablated patients.

In an in-depth look at the cost of AF ablation among Medicare patients followed for a year after ablation, Kim et al. found the cost of successful ablation at US$16,049 ± 12,536 versus US$19,997 ± 13,958 for failed ablation. Ablation was successful in 51% of the patients in his cohort, similar to our findings [31].

Four papers attempted to perform a cost-benefit analysis of AF ablation with that of medical therapy. In the first of these studies, a Markov decision analysis model looking at 55- and 65-year-old cohorts of patients at low and moderate risk of stroke was created by the investigators [32]. Complications and costs related to AF, medical therapy, and catheter ablation were accounted for. The model assumed that amiodarone would be used for rhythm control and a combination of digoxin and atenolol—for rate control. Eighty percent efficacy of AF ablation was assumed with 30% redo rate during the first year and 2% per year late success attrition rate. It was further assumed that as many as 38% of the patients on rate control would convert to sinus rhythm with annual AF relapse rate of 5%. Moderate risk of stroke was defined as having one risk factor, including diabetes, hypertension, coronary artery disease, or congestive heart failure. Patients at low risk of stroke were assumed to have no such risk factors. For the purpose of the model, patients at moderate risk of stroke were anticoagulated, whereas those at low risk could be on warfarin or aspirin. The model incorporated annual stroke risk of 2.3% and 1.1% for patients treated with aspirin and 1.3% and 0.7% for those on warfarin at moderate and low risk for stroke, respectively. A relative stroke risk of 1.4% per decade was accounted for. Age-adjusted mortality based on life tables and mortality reductions attributable to aspirin and warfarin were accounted for. All health care costs were calculated in 2004 US dollars using 3% discounting per year. Costs were estimated based on Medicare reimbursement rates, hospital accounting information, published literature, and the Red Book for wholesale drug costs. Catheter ablation appeared to be most cost-effective in younger patients at moderate risk of stroke at $28,700/QALY gained. It was somewhat less cost effective in the older moderate risk patients at $51,800/QALY gained and least cost-effective among the younger patients at low risk of stroke at $98,900/QALY gained. Unfortunately, since no evidence has been presented to date on the efficacy of ablation for prevention of thromboembolic events, the findings of this study are conditional on such evidence coming to light in the years to come.

Eckard et al. developed a decision-analytic model to estimate costs, health outcomes and incremental cost-effectiveness of RFA compared to AAD treatment for AF for a lifetime time horizon [33]. The authors used a decision tree for the initial year in which the RFA procedure is assumed to take place, and a long-term Markov structure for subsequent years. The authors factored in the potential for a second

ablation within a year of the first procedure in patients still suffering from AF. They assumed 70%–80% ablation success within the first year with 1.4 ablations per patient required to maintain rhythm based on Swedish data. The cost of ablation was estimated at around US$12,000, including the cost of 3-4 days in hospital, all diagnostic examinations necessary as well as the cost of disposables. Annual cost of AF therapy was estimated at US$2000. In order to estimate QALY weights for different health states, age-adjusted QALY weights based on a Swedish general population were applied for patients in the controlled AF state and used as reference points. A decrement of 0.1 for uncontrolled AF and 0.25 for stroke was applied to the baseline utility in the controlled AF state. With annual success attrition rates of 5%, 10%, and 15% used in the sensitivity analysis, the relative cost of ablation was estimated up to US$58000 per QALY without assuming stroke prevention related to the ablation strategy.

A similar analysis in the United Kingdom suggested incremental cost effectiveness of ablation at US$16,000 per QALY in 2008 dollars. The authors of this paper assumed freedom from AF at 84% at one year with 2%–4%/year rate of success attrition over time resulting in their estimates favouring ablation over the other published economic analyses. Further sensitivity analyses found the estimate to depend significantly both on the relative QOL estimate associated with sinus rhythm and on the prognostic implications of being in rhythm [34].

Finally in a more recent paper, Reynolds and his group published a Markov model cost-effectiveness analysis of ablation versus antiarrhythmic therapy in a simulated cohort of patients with paroxysmal drug refractory AF projected over 5 years. The authors assumed 60% success of the ablation approach with a 25% rate of repeat ablation. Utilities for QOL assessment were derived from real-life data, using the FRACTAL registry for the medically treated patients using SF-12 and patients ablated at the authors' institution as well as those enrolled in the A4 trial for derivation of the scores in this cohort based on the SF-36 questionnaire. In the base scenario, the incremental cost per QALY among ablated patients was US$47,333 with cost neutrality achieved at ~10 years [35].

This latter finding corresponds to the extreme variation in the model originally presented by Khaykin et al, where assuming actual clinical outcomes and costs incurred in the care of over 600 AF patients since 2004, the costs of ablation and medical therapy would be expected to reach parity at 6–9 years for patients with paroxysmal AF and at 8–15 years for patients with nonparoxysmal AF. Unfortunately, there is little well-reported data on AF followup greater than 5 years postablation, and significant advances in technology and medical therapy are typically seen over such an extended period with significant premium associated with new treatment modalities and little concurrent data on any associated clinical benefit over the standard of care. In this environment, exact relative costs of ablation and medical therapy remain elusive leaving us with reasonably well-grounded assumptions at best.

5. Global Perspective

While there is accumulating data from multiple geographies that ablation is both clinically superior and is economically feasible in certain populations, it may not be available globally. Furthermore, despite the advent of international practice guidelines, the care of AF patients, thresholds for application of therapies with an expensive upfront price tag such as ablation may vary dramatically from country to country and between population strata within any given geography. A good illustration of this principle is an in-depth analysis looking at the direct cost of AF care across several European countries for a prespecified patient (female aged <65 years with first-detected AF and no comorbidities at baseline) where costs varied from about US$1000 per year to US$2200 [36]. That said, reassuringly, the estimates of cost and cost effectiveness of ablation have been within close range of each other in Canada, the United States, and Europe using a variety of assumptions taken and sensitivity analysis performed, generally speaking supporting the claim of cost effectiveness of ablation.

6. Future Considerations

Several developments may impact our understanding of the cost effectiveness of AF ablation in the next decade. First and foremost, the techniques of AF ablation are constantly evolving and we have seen an unprecedented influx of new AF ablation technologies. While all published studies are based on the success of standard point-by-point AF ablation, and most long-term studies followed patients ablated using a solid tip catheter, the broader adoption of irrigated tip catheters in the last few years and new ablation technologies may change the landscape of AF ablation by substantially improving outcomes and reducing resources and operator training necessary to achieve success. Whether this would translate into improved economics of AF ablation will depend to a large extent on the incremental cost of these technologies in relation to incremental success or reduction in the rate of procedural complications.

New antithrombotic agents such as dabigatran may substantially reduce the cost related to anticoagulation management and may usher in an era of intermittent oral anticoagulation targeted to the time the patients actually spend in AF. This may substantially impact the cost of medical therapy, making it more attractive but would also improve the cost of the ablation strategy in patients who would no longer require preoperative bridging of their anticoagulation and will affect the cost of ongoing therapy in patients following ablation.

Similar considerations may apply to the new antiarrhythmic agents which, like dronedarone, may be less likely to cause long-term complications associated with this group of drugs in the past and therefore would be expected to improve the cost of medical therapy.

Finally, a large multicenter international trial, CABANA, will help us get a better understanding of the relative risks and benefits of ablation and medical therapy using "hard"

outcomes of death and stroke and will allow for a definitive cost-effectiveness analysis of AF ablation.

7. Conclusions

Atrial fibrillation clearly remains a significant medical disorder with far reaching social and economic implications. Despite significant advances in our understanding of this condition, we are far from having developed a perfect therapeutic strategy for AF. Several new agents that have entered the market show promise for reduction of morbidity and mortality related to this condition, while government initiatives are coming into place to streamline care and avoid preventable and costly negative health outcomes.

Several studies comparing ablation with medical therapy support the claim of short-term benefits related to the invasive therapy among patients with paroxysmal AF. At the same time, recent evidence suggests greater attrition of success among ablated patients over the long run than used in most of these studies. In this climate, previously published literature supporting long-term economic benefit of ablation has to be critically reassessed, and new models based on real life outcomes data need to be looked at to re-evaluate their findings.

Finally, evolution of ablation technologies, antiarrhythmic and antithrombotic agents, and large clinical trials comparing the impact of ablation and medical therapy on morbidity and mortality may radically change our understanding of the economics of AF ablation in the next few years.

References

[1] A. J. Camm and O. A. Obel, "Epidemiology and mechanism of atrial fibrillation and atrial flutter," *American Journal of Cardiology*, vol. 78, no. 8, pp. 3–11, 1996.

[2] D. Bialy, M. H. Lehmann, D. N. Schumacher, R. T. Steinman, and M. D. Meissner, "Hospitalization for arrhythmias in the United States: importance of atrial fibrillation," *Journal of the American College of Cardiology*, vol. 19, p. 41A, 1992.

[3] E. J. Benjamin, P. A. Wolf, R. B. D'Agostino, H. Silbershatz, W. B. Kannel, and D. Levy, "Impact of atrial fibrillation on the risk of death: the Framingham Heart Study," *Circulation*, vol. 98, no. 10, pp. 946–952, 1998.

[4] P. A. Wolf, R. D. Abbott, and W. B. Kannel, "Atrial fibrillation as an independent risk factor for stroke: the Framingham Study," *Stroke*, vol. 22, no. 8, pp. 983–988, 1991.

[5] D. J. Gladstone, E. Bui, J. Fang et al., "Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated," *Stroke*, vol. 40, no. 1, pp. 235–240, 2009.

[6] S. H. Hohnloser, D. Pajitnev, J. Pogue et al., "Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy. An ACTIVE W substudy," *Journal of the American College of Cardiology*, vol. 50, no. 22, pp. 2156–2161, 2007.

[7] A. S. Go, E. M. Hylek, K. A. Phillips et al., "Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study," *Journal of the American Medical Association*, vol. 285, no. 18, pp. 2370–2375, 2001.

[8] S. Stewart, N. Murphy, A. Walker, A. McGuire, and J. J. V. McMurray, "Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK," *Heart*, vol. 90, no. 3, pp. 286–292, 2004.

[9] I. Olivotto, F. Cecchi, S. A. Casey, A. Dolara, J. H. Traverse, and B. J. Maron, "Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy," *Circulation*, vol. 104, no. 21, pp. 2517–2524, 2001.

[10] S. Rambihar, P. Gao, K. Teo et al., "Heart rate is associated with increased risk of major cardiovascular events, cardiovascular and all-cause death in patients with stable chronic cardiovascular disease—analysis of ONTARGET/TRANSCEND," *Canadian Journal of Cardiology*, vol. 26, p. 76D, 2010.

[11] A. J. McDonald, A. J. Pelletier, P. T. Ellinor, and C. A. Camargo, "Increasing US emergency department visit rates and subsequent hospital admissions for atrial fibrillation from 1993 to 2004," *Annals of Emergency Medicine*, vol. 51, no. 1, pp. 58–65, 2008.

[12] K. S. Coyne, C. Paramore, S. Grandy, M. Mercader, M. Reynolds, and P. Zimetbaum, "Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States," *Value in Health*, vol. 9, no. 5, pp. 348–356, 2006.

[13] Information, C.I.f.H., "The Cost of Acute Care Hospital Stays by Medical Condition in Canada," CIHI, 2004-2005.

[14] D. G. Wyse, A. L. Waldo, J. P. DiMarco et al., "A comparison of rate control and rhythm control in patients with atrial fibrillation," *New England Journal of Medicine*, vol. 347, no. 23, pp. 1825–1833, 2002.

[15] J. Carlsson, S. Miketic, J. Windeler et al., "Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the strategies of treatment of atrial fibrillation (STAF) study," *Journal of the American College of Cardiology*, vol. 41, no. 10, pp. 1690–1696, 2003.

[16] S. H. Hohnloser, K. H. Kuck, and J. Lilienthal, "Rhythm or rate control in atrial fibrillation—pharmacological intervention in atrial fibrillation (PIAF): a randomised trial," *Lancet*, vol. 356, no. 9244, pp. 1789–1794, 2000.

[17] S. H. Hohnloser, H. J. G. M. Crijns, M. van Eickels et al., "Effect of dronedarone on cardiovascular events in atrial fibrillation," *New England Journal of Medicine*, vol. 360, no. 7, pp. 668–678, 2009.

[18] M. Haissaguerre, P. Jais, D. C. Shah et al., "Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins," *New England Journal of Medicine*, vol. 339, no. 10, pp. 659–666, 1998.

[19] K. Nademanee, J. McKenzie, E. Kosar et al., "A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate," *Journal of the American College of Cardiology*, vol. 43, no. 11, pp. 2044–2053, 2004.

[20] D. J. Wilber, C. Pappone, P. Neuzil et al., "Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial," *Journal of the American Medical Association*, vol. 303, no. 4, pp. 333–340, 2010.

[21] O. M. Wazni, N. F. Marrouche, D. O. Martin et al., "Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial," *Journal of the American Medical Association*, vol. 293, no. 21, pp. 2634–2640, 2005.

[22] P. Jais, B. Cauchemez, L. Macle et al., "Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study," *Circulation*, vol. 118, no. 24, pp. 2498–2505, 2008.

[23] A. N. Shah, S. Mittal, T. C. Sichrovsky et al., "Long-term outcome following successful pulmonary vein isolation: pattern and prediction of very late recurrence," *Journal of Cardiovascular Electrophysiology*, vol. 19, no. 7, pp. 661–667, 2008.

[24] D. Katritsis, M. A. Wood, E. Giazitzoglou, R. K. Shepard, G. Kourlaba, and K. A. Ellenbogen, "Long-term follow-up after radiofrequency catheter ablation for atrial fibrillation," *Europace*, vol. 10, no. 4, pp. 419–424, 2008.

[25] E. Bertaglia, C. Tondo, A. de Simone et al., "Does catheter ablation cure atrial fibrillation? Single-procedure outcome of drug-refractory atrial fibrillation ablation: a 6-year multicentre experience," *Europace*, vol. 12, no. 2, pp. 181–187, 2010.

[26] W. S. Tzou, F. E. Marchlinski, E. S. Zado et al., "Long-term outcome after successful catheter ablation of atrial fibrillation," *Circulation: Arrhythmia and Electrophysiology*, vol. 3, no. 3, pp. 237–242, 2010.

[27] Y. Khaykin, C. A. Morillo, A. C. Skanes, A. McCracken, K. Humphries, and C. R. Kerr, "Cost comparison of catheter ablation and medical therapy in atrial fibrillation," *Journal of Cardiovascular Electrophysiology*, vol. 18, no. 9, pp. 907–913, 2007.

[28] M. R. Reynolds, V. Essebag, P. Zimetbaum, and D. J. Cohen, "Healthcare resource utilization and costs associated with recurrent episodes of atrial fibrillation: the FRACTAL registry," *Journal of Cardiovascular Electrophysiology*, vol. 18, no. 6, pp. 628–633, 2007.

[29] K. Moeremans, E. Aliot, C. de Chillou, L. Annemans, C. le Pen, and P. de Jong, "Second line pharmacological management of paroxysmal and persistent atrial fibrillation in France: a cost analysis," *Value in Health*, vol. 3, no. 6, pp. 407–416, 2000.

[30] R. Weerasooriya, P. Jais, J. Y. Le Heuzey et al., "Cost analysis of catheter ablation for paroxysmal atrial fibrillation," *Pacing and Clinical Electrophysiology*, vol. 26, no. 1, pp. 292–294, 2003.

[31] M. H. Kim, J. Lin, C. Kreilick, and S. H. Foltz Boklage, "Total costs and atrial fibrillation ablation success or failure in medicare-aged patients in the United States," *Advances in Therapy*, vol. 27, no. 9, pp. 600–612, 2010.

[32] P. S. Chan, S. Vijan, F. Morady, and H. Oral, "Cost-effectiveness of radiofrequency catheter ablation for atrial fibrillation," *Journal of the American College of Cardiology*, vol. 47, no. 12, pp. 2513–2520, 2006.

[33] N. Eckard, T. Davidson, H. Walfridsson, and L. Å. Levin, "Cost-effectiveness of catheter ablation treatment for patients with symptomatic atrial fibrillation," *Journal of Atrial Fibrillation*, vol. 1, no. 8, pp. 461–470, 2009.

[34] C. McKenna, S. Palmer, M. Rodgers et al., "Cost-effectiveness of radiofrequency catheter ablation for the treatment of atrial fibrillation in the United Kingdom," *Heart*, vol. 95, no. 7, pp. 542–549, 2009.

[35] M. R. Reynolds, P. Zimetbaum, M. E. Josephson, E. Ellis, T. Danilov, and D. J. Cohen, "Cost-effectiveness of radiofrequency catheter ablation compared with antiarrhythmic drug therapy for paroxysmal atrial fibrillation," *Circulation: Arrhythmia and Electrophysiology*, vol. 2, no. 4, pp. 362–369, 2009.

[36] E. Holstenson, A. Ringborg, P. Lindgren et al., "Predictors of costs related to cardiovascular disease among patients with atrial fibrillation in five European countries," *Europace*, vol. 13, no. 1, pp. 23–30, 2011.