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Clinical and economic impact of first-line or drug-naïve catheter ablation and delayed second-line catheter ablation for atrial fibrillation using a patient-level simulation model

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ABSTRACT

Aims: To determine the clinical and economic implications of first-line or drug-naïve catheter ablation compared to antiarrhythmic drugs (AADs), or shorter AADs-to-Ablation time (AAT) in atrial fibrillation (AF) patients in France and Italy, using a patient level-simulation model.

Materials and methods: A patient-level simulation model was used to simulate clinical pathways for AF patients using published data and expert opinion. The probabilities of adverse events (AEs) were dependent on treatment and/or disease status. Analysis 1 compared scenarios of treating 0%, 25%, 50%, 75% or 100% of patients with first-line ablation and the remainder with AADs. In Analysis 2, scenarios compared the impact of delaying transition to second-line ablation by 1 or 2 years.

Results: Over 10 years, increasing first-line ablation from 0% to 100% (versus AAD treatment) decreased stroke by 12%, HF hospitalization by 29%, and cardioversions by 45% in both countries. As the rate of first-line ablation increased from 0% to 100%, the overall 10-year per-patient costs increased from €13,034 to €14,450 in Italy and from €11,944 to €16,942 in France. For both countries, the scenario with no delay in second-line ablation had fewer AEs compared to the scenarios where ablation was delayed after AAD failure. Increasing rates of first-line or drug-naïve catheter ablation, and shorter AAT, resulted in higher cumulative controlled patient years on rhythm control therapy.

Limitations: The model includes assumptions based on the best available clinical data, which may differ from real-world results, however, sensitivity analyses were included to combat parameter ambiguity. Additionally, the model represents a payer perspective and does not include societal costs, providing a conservative approach.

Conclusion: Increased first-line or drug-naïve catheter ablation, and shorter AAT, could increase the proportion of patients with controlled AF and reduce AEs, offsetting the small investment required in total AF costs over 10 years in Italy and France.

PLAIN LANGUAGE SUMMARY

This study created an individual patient level simulation to estimate the clinical and economic implications of catheter ablation, which is a non-pharmacological option to treat patients with atrial fibrillation (AF). This study examines the impact of the updated 2020 ESC guidelines to managing AF in Italian and French patients comparing antiarrhythmic drug treatment to first- and second-line catheter ablation. Differences in AF-related adverse events (AEs) such as stroke, hospitalization, cardioversions, and bleeding events were considered in the model to inform the overall per-patient costs. The model was tested with 50,000 patient simulations to limit random effects. The results of the patient simulation model revealed that as the frequency of utilizing first-line catheter ablation increased from 0% to 100% compared to pharmacological treatment, AEs were reduced in both countries, resulting in a slightly increased 10-year-per-patient cost. Additionally, for patients who fail first-line pharmacological treatment, those who receive second-line catheter ablation in the next year, versus a delay of one or two years, had the highest rate of cumulative controlled patient years on rhythm control therapy and the lowest AE rate by year 10 of the model. Overall, 10-year per-patient costs were similar, regardless

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of whether second-line ablation was delivered with no delay or a one-or two-year delay. In conclusion, increased use of first-line catheter ablation and earlier second-line catheter ablation can reduce the rates of adverse clinical events and increase the proportion of patients with controlled AF for a similar investment in per-patient costs over 10-years.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults, with the prevalence in Europe doubling over the last decade to about 2.0% of the total population[1,2]. Stroke is a key adverse event (AE) of AF, as the absence of organized atrial contraction enables the formation of thrombi in the atria[3]. Moreover, AF and heart failure (HF) frequently coexist and potentiate each other in a vicious circle as AF begets HF and HF begets AF[1] resulting is a mutually noxious association.

Catheter ablation is recognized as being an effective rhythm control strategy for patients with AF[1,4,5]. However, catheter ablation is not widely used in Europe with eligible patients. In a retrospective analysis of administrative databases in Italy that included all hospitalized patients diagnosed with AF, only 3.54% of patients had at least one catheter ablation[6]. This low rate of use may be based on the restricted availability and low level of referral to catheter ablation. Studies have shown that due to access issues, ablation treatment can take over a year to be conducted, with such delays being associated with higher rates of AF recurrence, progression to persistent AF, HF hospitalization, and death[7–9].

The value of ablation has been affirmed by the 2020 European Society of Cardiology (ESC) guidelines[1]. These guidelines included several notable changes with regards to the use of catheter ablation, particularly as a first-line treatment. In fact, the 2020 ESC guidelines recommend first-line catheter ablation to reverse left ventricular dysfunction in AF patients when tachycardia-induced cardiomyopathy is highly probable, regardless of their symptom status (class I recommendation). In addition, first-line catheter ablation of AF prior to the use of antiarrhythmic drugs should be considered in selected patients with heart failure and reduced left ventricular ejection fraction (class IIa) to improve survival and reduce HF hospitalization, in AF patients with brady-tachy syndrome to avoid pacemaker implantation (class IIa), and in select patients with paroxysmal AF (class IIa) or persistent AF without major risk factors for arrhythmia recurrences (class IIb) to improve symptoms. Although these are selected populations of AF patients, the absolute number of patients undergoing first-line catheter ablation could considerably increase in the near future considering that AF is the most common cardiac arrhythmia. Finally, the ESC guidelines continue to express class I recommendation for catheter ablation as a second-line option in patients with paroxysmal or persistent AF refractory or intolerant to antiarrhythmic drug (AAD) therapy to improve symptoms (class I). Recently, a large-scale Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial showed a significantly lower rate of AF recurrence and a lower AE rate over 48 months in patients who received catheter ablation compared to conventional medical therapy[10]. Furthermore, early intervention to achieve rhythmic control is known to reduce cardiac outcomes and long-term follow up and is preferable to usual care to avoid high-risk adverse events[11]. Based on all the available evidence and in line with the 2020 ESC guidelines, the recent 2024 European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on catheter and surgical ablation of atrial fibrillation further supports the use of catheter ablation as first-line treatment[5]. In fact, this document reports general agreement on the benefit of first-line catheter ablation in symptomatic patients with paroxysmal recurrent AF[5].

To understand the potential impact of these recommendation and the limitations in access to ablation, this study used a simulation model to examine the clinical and economic answers to the following questions:

1. What is the impact of increased use of first-line or drug-naïve ablation instead of AAD therapy on long-term AF costs and clinical outcomes?
2. How does AADs-to-Ablation time (AAT), defined as the time interval between initiation of AADs as first-line treatment to control AF and the catheter ablation procedure, affect long-term AF costs and clinical outcomes?

Methods

Model design and parameters

An individual patient-level simulation model was developed in Microsoft Excel 2016. The total number of AF patients at the start of each analysis was 167,390 for Italy and 162,707 for France, based on each country's total population and the region-specific AF incidence rate[12,13]. The total number of incident AF patients (total starting diagnosed cohort) is calculated by multiplying the age and sex specific AF incidence rates by the population estimates for the region. Italy and France were selected as the countries for the analyses due to availability of costing data. In an individual patient-level simulation model, outcomes are modelled for individuals in the whole population of patients with AF whose clinical characteristics are randomly selected based on data sourced from the literature[14]. The model follows the clinical pathway of each patient and then aggregates the results (i.e. costs, AEs) for all simulated patients. The model considered the incidence of AF by disease type (paroxysmal, persistent, long-standing persistent, or permanent), and included common treatments (i.e. rate control and rhythm control therapies). During the time horizon patients may have experienced AF-associated AEs, including stroke, HF

hospitalization, or bleeding events, or may have received a cardioversion. The cycle length of the model was one year, and costs and outcomes were calculated over a 10-year time horizon. Half-cycle corrections were conducted for costs, but not outcomes. It was assumed that if a patient died in a model cycle in which they experienced an AF-AE, they most likely died as a result of that AE. Therefore, acute AE events were not half-cycle corrected, and the model assumed that all events occurred prior to death.

The model assigned patient characteristics and treatments, as well as simulated the probability of disease progression and event occurrence. Model parameters are provided in Supplementary Table 1 and Supplementary Table 2[10,15–41]. Each patient entering the model was randomly assigned individual characteristics (e.g. age, sex, HF status) based on population data. All patients in the analyses were assumed to be diagnosed and have symptomatic AF; the initial distribution of patients across disease types is outlined in Supplementary Table 2. All paroxysmal, persistent, and long-standing persistent patients were assumed to be receiving rhythm control therapy (with or without concomitant rate control therapy) (Figure 1). All progression, disease and treatment events were informed by evidence-based probabilities and chance, represented by a random number calculated for each patient for each model event.

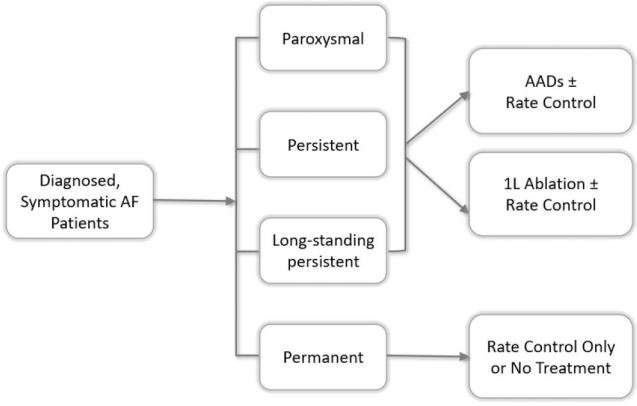

Figure 1. Model disease classification and treatment selection process.
Notes: All patients in the analyses were assumed to be diagnosed and symptomatic.
Abbreviations. 1L, first-line; AAD, antiarrhythmic drug; AF, atrial fibrillation.

Several studies were used to model different outcomes while prioritizing data from the CABANA trial, given that it is a recent, large, high-quality randomized controlled trial (RCT) comparing catheter ablation to drug therapy[10]. Remaining model parameters that could not be obtained from the CABANA trial were obtained from published studies[15–19,42–52]. To reflect the CABANA trial population, no patients were assigned an initial permanent AF type, but patients could progress to permanent AF in subsequent years in the simulation. As per the CABANA trial data, the yearly probability of arrhythmia recurrence following AAD therapy or catheter ablation varied by AF disease type. The annual probability of AF disease progression was informed by a registry study by Potpara et al.[15] and also varied by disease type and whether AF was controlled or uncontrolled.

Upon rhythm control therapy initiation, patients were assigned to receive either AAD therapy, or first-line catheter ablation based on our defined analysis questions. Treatment pathways for patients assigned to each of these rhythm control therapy options are shown in Figure 2. For patients assigned to AAD therapy, simplifying assumptions were made that:

1. All dose titrations and drug switches would occur within the first year of treatment;
2. After one year (one model cycle) of treatment with AADs, treatment would have been a success (controlled AF) or would have failed (uncontrolled AF); and
3. After successful treatment in year one, a proportion of patients would become uncontrolled the following year and in each subsequent year. In the case of AAD therapy failure (either after 1 year or after 2+ years), there was a probability of receiving second-line catheter ablation in a subsequent year.

For patients receiving catheter ablation, sequential ablations were not individually modelled but instead, the cost of catheter ablation included a proportion (9%) of patients expected to receive a second ablation procedure[17]. Subsequent ablation procedures beyond a year were not modelled as they are uncommon[17]. Following either first- or second-line catheter ablation, treatment was assumed to be

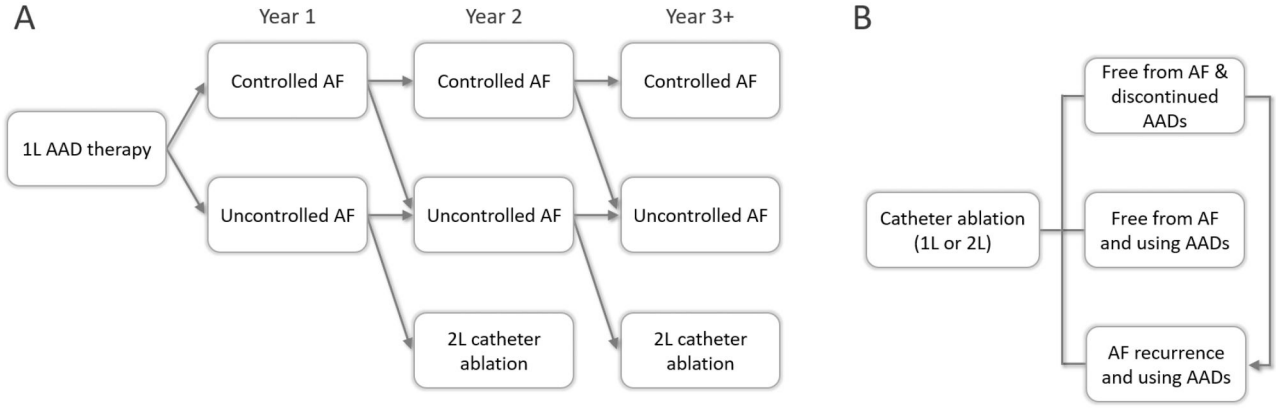

Figure 2. Treatment pathway for patients receiving AAD therapy (A) or catheter ablation therapy (B).
Abbreviations. 1L, first-line; 2L, second line; AAD, antiarrhythmic drug; AF, atrial fibrillation.

a success (controlled AF) or have failed (uncontrolled AF) – treatment success was dependent on disease type (92.3% of paroxysmal patients had controlled AF following a first- or second-line catheter ablation procedure versus 83.3% of persistent and long-standing persistent patients). Patients in which treatment was a success could either continue or discontinue AAD use depending on the treatment assumptions in the scenario. After successful ablation, arrythmia could re-occur, based on a probability of becoming uncontrolled each year. Patient treatment pathways can be visualized in Figure 2 and probabilities of health state transitions are outlined in Supplementary Table 2.

The probability of occurrence of AF-related AEs, including ischemic stroke, HF hospitalization, or bleeding event hospitalizations, as well as cardioversions, were influenced by a patient's AF treatment type and controlled/uncontrolled AF status (Supplementary Table 3). For those patients in which rhythm control therapy failed (uncontrolled AF), a HR of 1.6 is applied to general population age- and sex-specific stroke rates to account for an increased risk of stroke[45,46,53]. Patients who suffered a disabling stroke incurred an annual cost of disability in each year following the year of the index stroke event. All patients in the model had a probability of having HF. All AF-patients with HF have a probability of first HF hospitalization, and a probability of readmission for HF. The model allows for a decreased probability of first HF-admission for patients who have received catheter ablation therapy as per the CASTLE-AF study which showed an increased probability of freedom from HF hospitalization admission for patients who received ablation versus medical therapy[49]. The model assumed 83.7% of patients were using oral anticoagulants (OACs) for prevention of thromboembolic events regardless of whether they were successfully ablated[18]. Sensitivity analyses explored lowering OAC use among successfully ablated patients (controlled AF). It was assumed that only patients using OACs were at risk of a bleeding event hospitalization. Additionally, all uncontrolled AF-patients had an annual probability of receiving a cardioversion. In each model cycle, a patient had a probability of death as per general population mortality rates[54,55] and AF-related AEs[45,50,52].

Analysis 1: probability of first-line or drug-naïve catheter ablation

These analyses compared hypothetical scenarios of treating 0%, 25%, 50%, 75% or 100% of patients with first-line or drug-naïve catheter ablation and the remainder with AADs.

Analysis 2: time to second-line catheter ablation/AADs-to-ablation time (AAT) scenarios

Delivery of catheter ablation can be delayed due to budgetary or system constraints, since both Italy and France operate under a public healthcare system, surgical delays can occur due to resource availability. In fact, a real-world evidence Italian study on administrative databases of the years 2011–2019 revealed that AF ablation was performed in only 3.54% of overall patients hospitalized for AF with an average delay of 7.6 (SD: 13.4) months from AF diagnosis and ablation procedure [6]. Moreover, an observational Italian study undertaken in 2016 for 12 weeks confirmed that catheter ablation for AF was performed in only 3.8% of the patients hospitalized for AF[56]. In all treatment scenarios, first-line rhythm control therapy was 100% AADs (i.e. no first-line ablation). For patients that failed AADs, the probability of transitioning to second-line ablation was set to 100% and occurred in the next year or was delayed 1 or 2 years.

Outcomes

For each analysis question, number of patient-years with controlled AF, number of clinical AEs, and 10-year per-patient costs for AF therapy and its AEs were reported. Costs included the cost of medications (rate control drugs, AADs), catheter ablation, OACs, strokes, bleeding events, HF hospitalizations, cardioversions, and treatment-related AEs associated with catheter ablation and AADs. Only catheter ablation-related AEs resulting in new hospitalizations were considered in the model to avoid double counting the cost to the healthcare system for the catheter ablation procedure visit, since one diagnosis-related group (DRG) code is used per hospital visit. The model calculated direct costs from the perspective of the healthcare system – published cost data were used where possible. In the absence of published costs, costs by DRG code were used to inform the cost of ablation – DRG code 518 was used for Italy, and a weighted average cost of DRG codes 05K191, 05K192, 05K193, and 05K194 for procedure codes DEPF014 and DEPF033 were used for France. The DRG codes utilized represent the cost that the healthcare system is reimbursed, not the true cost of the procedure, which may vary based on ablation technique. Different ablation techniques are typically guided based on the patient's clinical baseline characteristics (i.e. comorbidities) which was not controlled for in this simulation. Costing sources are detailed in Supplementary Table 1. A discount rate of 3.0% was used for Italy[57] and 2.5% for France[20]. Non-DRG code costs were adjusted to 2022 euros[58]. Each analysis was run with 50,000 simulations to limit random effects and produce stable results. After 3,000 simulations, the total 10-year per-patient costs changed by less than 1% of the rolling average.

Sensitivity analyses

Four sensitivity analyses were conducted to explore the impact of alternative data sources on the model results (Supplementary Table 4). A sensitivity analysis with modified OAC usage was performed to reflect real-world patient discontinuation of treatment after successful ablation. Arbelo 2017 [24] reports OAC usage in 83.7% of patients prior to ablation (representing the base case scenario), however, after 12-month follow-up post-ablation, only 59.3% of patients were utilizing OAC medical management (representing sensitivity scenario one). The second sensitivity analysis assessed the impact of using alternative RCT data reported by Pappone et al.[59] to inform the annual probability of

recurrence following first-line AAD therapy or ablation. The third sensitivity analysis (analysis 1 only) used real-world data from the EORP-AF Pilot registry for the percentage of patients transitioning from AADs to ablation according to their AF subtype[21]. These percentages were considerably smaller compared to the base case inputs obtained from the CABANA trial. This third sensitivity analysis was not conducted for analysis 2 because the probability of transitioning from AADs to second-line ablation was set to 100% in this analysis. The fourth sensitivity analysis assessed the impact of modifying the percentage of patients controlled after one year of first-line AAD therapy. In the base case analyses, AAD recurrence was informed by Wazni[16] and Mont[17] since these articles reported recurrence data for each AF subtype, whereas the CABANA trial reported overall recurrence results. This sensitivity analysis examined the impact of sourcing AAD recurrence from the CABANA trial[10].

Results

Analysis 1: probability of first-line or drug-naïve catheter ablation

Treatment scenarios with higher rates of first-line or drug-naïve catheter ablation displacing first-line AAD therapy yielded more cumulative patient-years of controlled AF and fewer strokes, HF hospitalizations, and cardioversions (Figure 3). In the Italian scenario, a move from 0% to 100% first-line ablation decreased stroke by 12.0%, HF hospitalization by 29.0%, and cardioversions by 45.8% over 10 years (Figure 4A). Similarly, changing from 0% to 100% first-line ablation in the French scenario, stroke decreased by 12.2%, HF hospitalization by 28.8%, and cardioversions by 45.2% over 10 years (Figure 4B). For both the Italian and French scenarios, bleeding events remained relatively unchanged, as OAC use was consistent among patients receiving either rhythm control therapy. As the rate of first-line ablation increased from 0% to 50% and 100%, the 10-year per-patient costs increased in Italy (€13,034, €13,764, and €14,450 respectively) and in France (€11,944, €14,454, and €16,942, respectively), with the added costs of ablation partially offset by lower stroke, cardioversions, and HF hospitalization costs (Supplementary Table 5). Key 10-year results for Analysis 1 are presented in Table 1.

The model was robust to changes in parameters in the sensitivity analyses (Supplementary Table 6). In the first sensitivity analysis (modified OAC usage), changing from 0% to 100% first-line ablation resulted in a total 10-year per-patient cost increase of €546 in Italy and €3,636 in France. In the second sensitivity analysis (alternative AF recurrence probability after rhythm control treatment), the change from 0% to 100% first-line ablation resulted in a total 10-year per-patient cost increase of €748 and €4,598 in Italy and France, respectively. In the third sensitivity analysis (alternative percentage transitioning from AAD to ablation), changing from 0% to 100% first-line ablation resulted in a total 10-year per-patient cost increase of €1,588 and €4,598 in Italy and France, respectively. Lastly, in the fourth sensitivity analysis

Figure 3. Analysis 1 – cumulative years controlled on first-line ablation, second-line ablation and AADs, over the 10-year time horizon. (A) Italy. (B) France.
Abbreviations. 1L, first-line; 2L, second-line; AADs, antiarrhythmic drug; AF, atrial fibrillation.

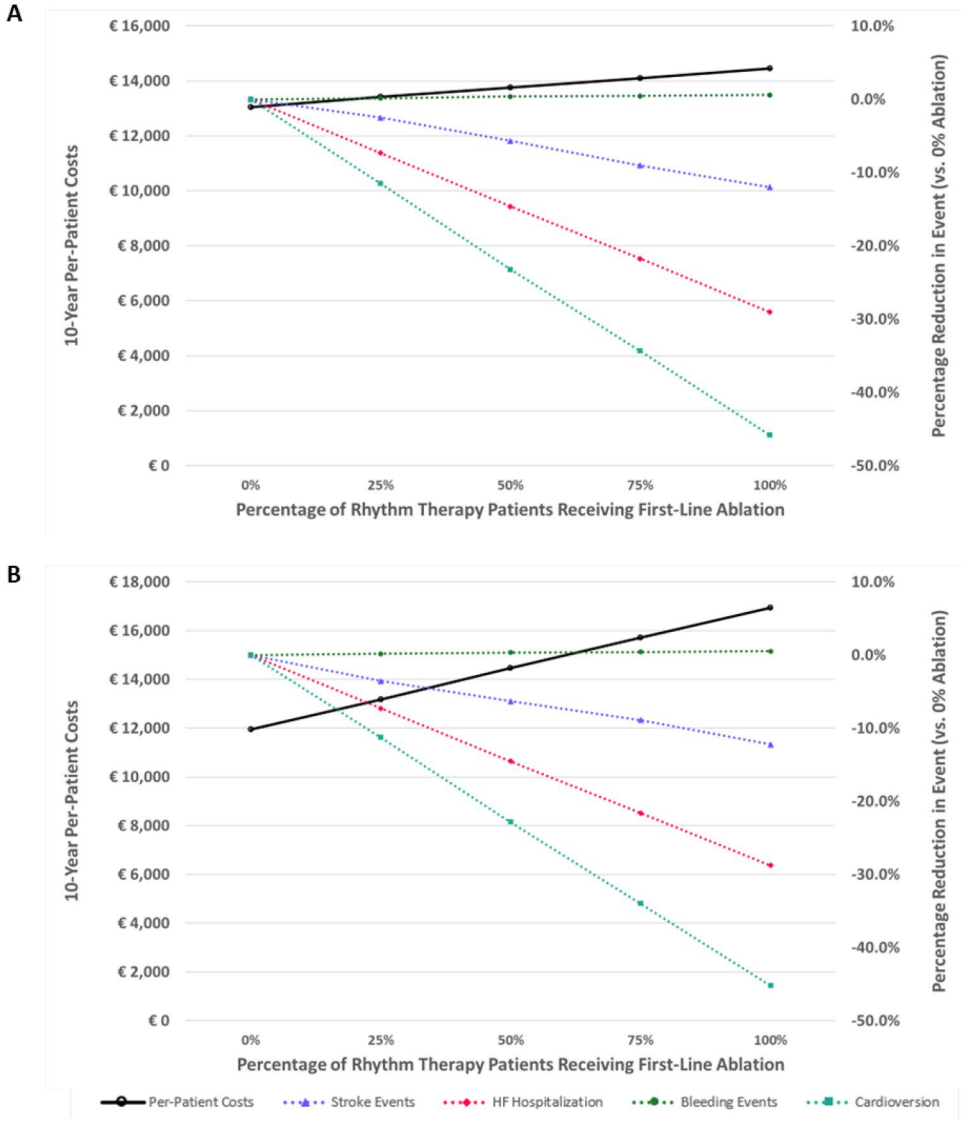

Figure 4. Analysis 1 – 10-year per patient costs and relative percent reduction in cumulative 10-year clinical events (versus 0% ablation) by treatment scenario. (A) Italy. (B) France.
Abbreviations. HF, heart failure.

Table 1. Key 10-year results for analysis 1: Probability of first-line or drug-naïve catheter ablation.

Treatment scenario: % 1L ablation	Cumulative years with controlled AF on rhythm therapy	Stroke events	HF hospitalizations	Bleeding events	Cardioversions	Per patient costs
Italy						
0%	388,915	24,955	100,397	24,961	77,482	€ 13,034
25%	473,874	24,329	93,022	24,991	68,556	€ 13,418
50%	561,508	23,538	85,684	25,052	59,481	€ 13,764
75%	646,673	22,698	78,543	25,072	50,873	€ 14,090
100%	733,468	21,962	71,238	25,105	41,968	€ 14,450
France						
0%	402,010	9,896	104,572	25,711	79,938	€ 11,944
25%	489,517	9,544	96,951	25,757	70,911	€ 13,179
50%	579,068	9,271	89,365	25,796	61,659	€ 14,454
75%	666,851	9,017	81,959	25,818	52,776	€ 15,717
100%	755,686	8,685	74,487	25,844	43,814	€ 16,942

Abbreviations. 1 L, first-line; AF, atrial fibrillation; HF, heart failure.

(alternative percentage of patients controlled after one year of first-line AAD therapy), the increase from 0% to 100% first-line ablation led to a total 10-year per-patient cost increase of €1,657 and €5,153 in Italy and France, respectively.

Analysis 2: time to second-line catheter ablation/AADs-to-ablation time (AAT) scenarios

Among the second-line ablation scenarios over the 10-year time horizon, for both Italy and France, the one with second-line catheter ablation delivered in the year after AAD failure

(i.e. AAD failure in year 1, ablation in year 2) with no delay (versus with 1 or 2 years delay with ablation occurring in years 3 or 4 respectively) had the highest cumulative years of controlled AF (Figure 5). It had lower stroke events, HF hospitalizations, and cardioversions compared to the scenarios where ablation was delayed by 1 or 2 years (Figure 6). The overall 10-year per-patient cost was similar across treatment scenarios, regardless of whether second-line ablation was delivered with no delay or a one- or two-year delay, for both Italy (€13,739 to €13,832 and €13,799) and France (€15,249 to €14,879 and €14,495). The 10-year per-patient costs of treatment and clinical AEs are presented in Supplementary Table 7. Key 10-year results for Analysis 2 are presented in Table 2.

The model was robust to changes in parameters in the sensitivity analyses (Supplementary Table 8). Overall, 10-year per-patient costs associated with no delay in second-line ablation were consistent across the three sensitivity analyses for both Italy (€13,542, €13,861, and €13,483) and France (€14,756, €15,604, and €14,904). Overall, 10-year per-patient costs when second-line ablation was delayed by 2 years were also similar across the three sensitivity analyses for both Italy (€13,816, €14,100, and €13,493) and France (€14,345, €14,925, and €14,157).

Discussion

The results of the study indicate that increased use of first-line catheter ablation and earlier second-line ablation generally result in fewer simulated stroke events, HF hospitalizations, and cardioversions and represent a small incremental cost compared to AAD therapy. Despite more patients receiving ablation and the higher cost of the ablation procedure compared to AADs, the reduction in clinical events offset the increased cost associated with ablation.

These results are consistent with the existing body of evidence demonstrating the clinical benefits of first-line and second-line ablation[7–9,60]. First-line radiofrequency catheter ablation has been associated with lower rates of symptomatic AF after 24 months compared to AAD therapy[61]. Increasing the duration between AF diagnosis and catheter ablation has been shown to be associated with higher rates of AF recurrence and hospitalizations[8,60].

In addition, the clinical and economic benefits of catheter ablation compared to drug therapy observed in this study are generally consistent with current guidelines and published literature. Based on evidence from RCTs and systematic reviews, the 2020 ESC guidelines for the management of AF state that catheter ablation is a safe and superior alternative to AADs for rhythm control[1]. The CABANA trial reported that catheter ablation was associated with lower rates of death and cardiovascular hospitalizations relative to AAD treatment[10]. Several observational studies also support the results of this trial. A large observational study based on claims data demonstrated an association between treatment with catheter ablation and a lower risk of thromboembolic events, including ischemic stroke, compared to patients using AADs[62]. Furthermore, a meta-analysis of RCT and real-world evidence data found that ablation was associated with a significantly reduced risk of death, stroke, and hospitalization compared with AADs and/or rate control drug therapy alone, suggesting that ablation prevents AF recurrence and improves long-term prognosis of AF patients[63]. These findings from the literature support the reduction in stroke events and HF hospitalizations observed in the model when a greater proportion of simulated patients received first-line ablation or earlier second-line ablation.

Figure 5. Analysis 2 – cumulative years controlled on second-line ablation and AADs, over the 10-year time horizon. (A) Italy. (B) France.
Abbreviations. 2L, second-line; AADs, antiarrhythmic drug; AF, atrial fibrillation.

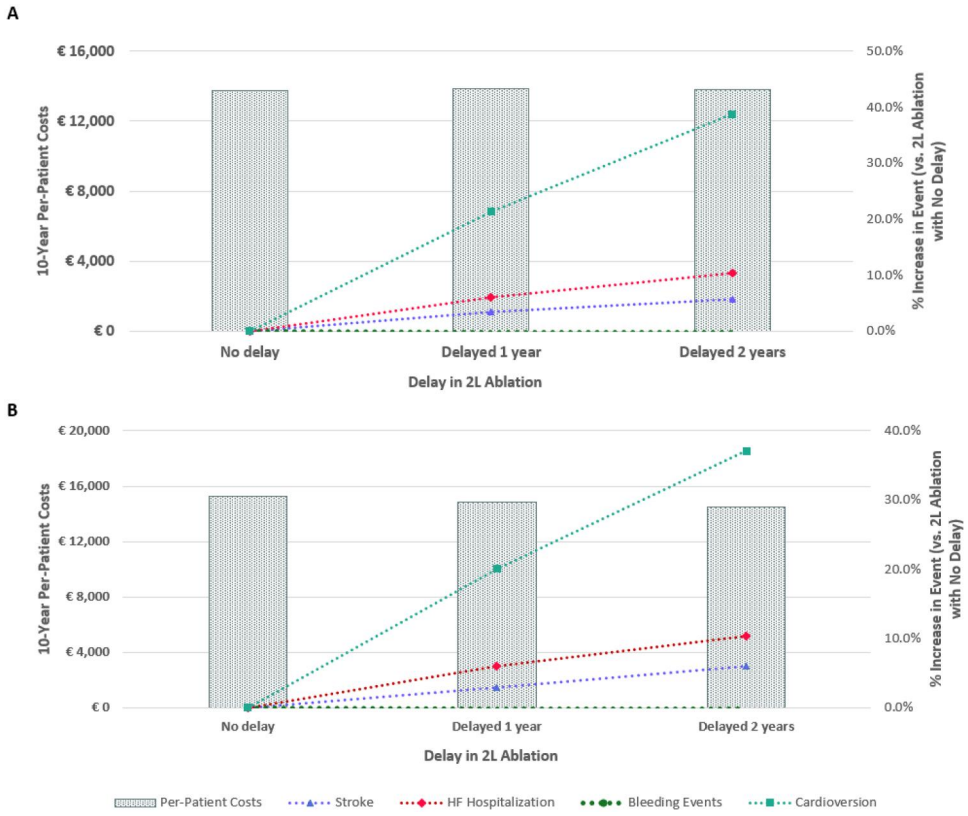

Figure 6. Analysis 2 – 10-year per patient costs and relative percent increase in cumulative 10-year clinical events for scenarios where there is no delay in second-line catheter ablation following failure of AADs versus a delay of one or two years in second-line catheter ablation upon failure. (A) Italy. (B) France.
Abbreviations. 2L, second-line; HF, heart failure.

Table 2. Key 10-year results for analysis 2: Time to second-line catheter ablation / AADs-to-ablation time (AAT) scenarios.

Treatment scenario	Cumulative years with controlled AF on rhythm therapy	Stroke events	HF hospitalizations	Bleeding events	Cardioversions	Per patient costs
Italy						
2L ablation with no delay	737,794	21,637	87,451	25,035	40,950	€ 13,739
2L ablation delayed 1 year	654,051	22,373	92,748	24,998	49,688	€ 13,832
2L ablation delayed 2 years	582,539	22,872	96,524	24,971	56,819	€ 13,799
France						
2L ablation with no delay	766,376	8,539	90,888	25,766	42,226	€ 15,249
2L ablation delayed 1 year	683,890	8,783	96,410	25,730	50,683	€ 14,879
2L ablation delayed 2 years	611,414	9,047	100,283	25,730	57,888	€ 14,495

Abbreviations. 2 L, second-line; AF, atrial fibrillation; HF, heart failure.

While this model only considered the economic and clinical burden of ablation, the cost-effectiveness of catheter ablation is also supported by the literature. A cost-effectiveness analysis of catheter radiofrequency ablation versus AADs for first-line treatment of paroxysmal AF found that first-line radiofrequency ablation was cost-effective in patients 50 years of age or younger at €3,434 per additional quality-adjusted life years gained[46]. Similarly, a 2022 cost-effectiveness analysis using real-world data from the United Kingdom found that catheter ablation had a favourable incremental cost-effectiveness ratio of £8,614 per quality-adjusted life year gained compared to medical therapy in patients with AF[64]. These findings confirm previous analyses conducted in the United Kingdom using data from clinical trials, which found radiofrequency catheter ablation to be the most cost-effective type of ablation technology compared to AADs[65]. Furthermore, a real-world Italian claims database analysis reported that catheter ablation results in significantly better clinical outcomes and a significant reduction in health-care resource utilization and associated costs[6].

Limitations

There were several limitations due to data uncertainty or availability. Firstly, the current model parameters are specific to the Italian and French healthcare system, and therefore findings may not be generalizable to other geographic locations. However, the model has the flexibility to be adapted to any other country that utilizes a public healthcare system, based on data availability for the country of interest. In addition, the model made assumptions regarding disease progression based on the best available clinical data. For example, uncontrolled patients were assumed to be able to progress to more persistent AF types but not improve, while controlled patients were able to regress to less persistent AF types. Practice patterns were simplified such that paroxysmal,

persistent and long-standing persistent AF patients were all assigned the same initial treatment pattern, as reported in the EORP-AF Pilot General Registry[21]. Of note, annual probabilities of progression to more persistent AF types may be underestimated as rates of disease progression were informed through an observational cohort study ($N = 346$) of patients with lone AF of a relatively young age (mean age = 43.2 years). Although the annual probability of disease progression may be underestimated, controlled and uncontrolled AF status is largely dependent on the type of rhythm control (i.e. AADs versus ablation), rather than disease type[10,16,17,66]. Further, it was assumed that efficacy of ablation was consistent regardless of the duration of uncontrolled AF. For example, patients who had no delay in receiving second-line ablation upon AAD failure had the same probability of treatment success as those who had a delay in second-line ablation of 2 years. In the real world, patients with longer durations of uncontrolled AF may be less likely to respond to ablation and have controlled disease. However, current literature sources and the 2020 ESC guidelines have yet to quantify the impact disease progression can have on procedural success, as there are a variety of confounding comorbidities (i.e. obesity, hypertension, smoking, etc) that also play a role in dictating ablation referral and success[1].

Moreover, this model may have been conservative in calculating disease costs, as there may be some outpatient costs associated with clinical events and hospitalizations due to AF itself that were not captured in this simulation. Although excluding costs related to outpatient care and certain hospitalizations associated with AF may underestimate the overall cost of care, due to this data not being well-reported within the literature and the variability in these outcomes amongst patients, it would be difficult to accurately simulate these within the model. The model does however include costs associated with AEs as reported in the CABANA trial, such as ischemic stroke, HF hospitalization, bleeding event hospitalizations, and cardioversion. Since the model adopted a public healthcare payer perspective, many AE costs were informed by DRG tariffs and, as such, the costs reported in this study may not reflect the entirety of expenses incurred by hospital centres. In addition, the model did not include out-of-pocket costs incurred by patients or indirect costs to society such as the cost of lost patient productivity and caregiver costs. However, if additional expenses related to clinical events are to be incurred in the real world, cost-savings from a reduction in clinical events with increased use of first-line ablation or performing the procedure earlier would be more favourable than predicted. In fact, a recent real-world analysis conducted in Italy found that ablation was associated with a significant improvement in post-operative outcomes and a significant reduction in healthcare-related costs[6]. The difference in cost impact reported in this study and the current model may therefore be explained by some costs, such as the cost of AF-related hospitalizations, not being captured in this simulation.

Further, the current time horizon explored in this study may not be sufficient to capture all AEs an AF patient may experience in their entire lifetime, as this only provides a 10-year time horizon. While the results presented show a similar investment in total AF costs when comparing catheter ablation to AADs, these results cannot be extrapolated past the 10-year time horizon with certainty. Simulating patient outcomes longer than 10-years may not be accurate as there are a multitude of variables that can change within an extended time horizon, such as ablation technologies, changes in reimbursement, changes in patient profiles due to preventative medicine, early diagnosis and treatment of co-morbidities. An observational study of patients with AF who received AF catheter ablation and were followed for 10-years shows that on a long-term follow-up the maintenance of sinus rhythm depends on the lack of increase with respect to baseline of body mass index (BMI), blood pressure, and fasting plasma blood glucose[67]. This shows that AF is a dynamic condition during the long-term follow-up, as the long-term outcome does not necessarily depend on the procedures performed in a given patient, but on the progression of other co-morbidities (i.e. obesity, hypertension, diabetes).

Lastly, the model results rely on parameter estimation based on the literature and real-world results may differ from published data. However, several sensitivity analyses were conducted to explore the impact of varying variable input values found that results were robust to parameter uncertainty. While some treatment scenarios, such as 100% first-line ablation or 100% second-line catheter ablation following AAD failure, are not necessarily realistic and unlikely to be implemented in clinical practice, they aim to explore the impact of possible treatment options to inform future research and policy discussions on AF treatment management.

Conclusion

Increased use of catheter ablation for first-line or drug-naïve rhythm control therapy and avoiding delays in second-line catheter ablation after first-line AAD failure in a simulated model increased the proportion of patients with controlled AF and reduced clinical AEs for a similar investment in total AF costs over ten years in Italy and France. Further research on the long-term outcomes of AF patients could better inform healthcare payers, clinicians, and patients on the potential value of this treatment strategy.

Transparency

Declaration of funding

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Declaration of financial/other relationships

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financial relationships or otherwise to disclose. The Editors in Chief helped with adjudicating the final decision on this paper.

Author contributions

LC, LP, and DG are employees of EVERSANA which was contracted by Biosense Webster to develop the model and help write the manuscript. GC is an employee of Biosense Webster who provided funding for the study and who manufacture catheter ablation devices. MH is an employee of Johnson & Johnson Medical.

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