Effectiveness of catheter ablation of atrial fibrillation in Belgian practice: a cohort analysis on administrative data

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Aim
To assess the outcome and cost of catheter ablation of atrial fibrillation (AF) in Belgium.

Methods and results
From a nationwide health insurers’ database, we retrieved claims data of all patients that underwent a catheter ablation of AF from November 2007 through December 2008. Based on data on reimbursed procedures and drugs, we assessed AF recurrence using different models. Costs related to the index hospitalization were calculated. During the observation period, 830 patients underwent a first catheter ablation of AF. Two-year follow-up data were available for all patients, with an average follow-up of 30.2 months. Seventy-seven percent of patients were treated for paroxysmal AF. Recurrence of AF was defined as the occurrence of one of the following events: a repeat catheter ablation, an electric cardioversion or an antiarrhythmic drug (AAD) prescription, the latter two taking into account a blanking period of 3 months. Atrial fibrillation recurred in 59.8% of patients after 1 year and in 65.9% of them after 2 years. If AAD prescription was considered as an indicator for ablation failure only if it occurred after a 1 month AAD-free period, recurrence of AF occurred in 37.3% of patients after 1 year and in 49.9% after 2 years. Based on the prescription of rate and rhythm control drugs before the ablation, we conclude that up to 15.8% of patients underwent catheter ablation as first-line therapy. Catheter ablation of AF in Belgium on average costs about €9600 for the initial intervention.

Conclusion
Since the effectiveness of catheter ablation of AF appears to be less favourable in real-world practice as compared with results reported in clinical trials, and given the high initial cost of the procedure, we suggest to strictly limiting the intervention to patients in whom it is currently believed to be most beneficial, i.e. those with severely symptomatic and drug-refractory paroxysmal AF with no or minimal structural heart disease.

Keywords
Atrial fibrillation • Catheter ablation • Administrative database • Health technology assessment

Introduction
From both clinical trials and observational studies, it appears that there is a profound variance in the reported effectiveness of catheter ablation of atrial fibrillation (AF). This variance may be related to several factors such as patient selection, definition of success, the use of different techniques, or uneven experience across centres.

In November 2007, new reimbursement rules for electrophysiology were introduced in Belgium allowing the precise identification of the cardiac arrhythmia for which the electrophysiology procedure was performed. By then, physician’s fees and devices used for AF ablation together were reimbursed at €4970 per case. The number of ablations of AF more than doubled from <1000 before 2008 up to >2000 procedures in 2010, for a population of 11 million inhabitants. In the context of a health technology assessment of catheter ablation of AF that was commissioned by the Belgian government, we analysed the outcome of patients that were treated from November 2007 through December 2008.

Methods
Data were abstracted from the Intermutualistic Agency (IMA) database which contains population and reimbursement data from the members of the seven Belgian sickness funds. For the purpose of this study, IMA

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provided detailed reimbursed healthcare provisions, drugs delivery, and population data, covering the years 2006–2010, of patients who underwent a catheter ablation for AF between 1 November 2007 and 31 December 2008. Patients were included in our study only if they had no previous catheter ablation procedure between 1 January 2006 and 31 October 2007, suggesting that the ablation of interest was the first such procedure in a given patient. It is further referred to in this paper as the index ablation.

The IMA database does not contain clinical data. Some aggregated patient data were, however, available from the catheter ablation registry of the Belgian Heart Rhythm Association that contains records of 5546 AF ablation procedures performed between 2008 and 2011. These data were used to establish the proportion of patients who were treated for paroxysmal or non-paroxysmal (i.e. persistent or long-standing persistent) AF.

We analysed drug use before and after the index ablation. Antiarrhythmic drugs (AADs) were defined as those belonging to level C01B (AADs, class I and III) of the Anatomical Therapeutic Chemical (ATC) classification system (WHO Collaborating Centre for Drug Statistics Methodology). Rate control drugs were ATC classes C07 (beta blocking agents), C08DA01 (verapamil), C08DB01 (diltiazem), or C01AA (digitalis glycosides). We performed an additional separate analysis for sotalol (C07AAD7), since it has both rate and rhythm control properties.14

A patient was considered having followed a given drug treatment when he received at least one delivery of it. We took into account a blanking period of 3 months, representing a time window traditionally accepted as a period during which the ablation scar has to heal, and during which recurrent AF is not considered a failed ablation.

Patients were considered at high risk for future events if they were on maintenance anticoagulation therapy prior to the ablation. This assumption is based on the recommendation from international guidelines that patients at high risk for thrombo-embolic complications should be treated with anticoagulants.

To identify patients in whom catheter ablation was used as a first-line treatment of AF, we assessed whether they were prescribed a rate and a rhythm control drug during the observation period preceding the index ablation. Since amiodarone and sotalol have both rate and rhythm control properties, we accepted their use as a single agent qualifying for both treatment modalities. If a patient did not at least temporarily used amiodarone, or sotalol, or a combination of a non-amiodarone AAD and a non-sotalol rate control drug, the procedure was considered being performed as a first-line treatment.

The use of electric cardioversions in every patient was identified before and after the index catheter ablation.

To estimate the 2 year effectiveness of the index ablation in the target population, we defined a number of events that we considered indicating a failure, and introduced them in a Kaplan–Meier time-to-event analysis. This was conducted by using SAS version 9.3 (SAS Institute Inc, North Carolina, USA). We regarded any redo ablation a failure of the index procedure. We also considered it failed if a patient underwent an electric cardioversion or used an AAD beyond the blanking period of 3 months. We envisaged two additional models to assess the effectiveness of the ablation. In one, AAD use was counted as indicating a failed ablation only if it started after a drug-free period of at least 1 month beyond the blanking period. Another model was constructed where this additional drug-free month was considered for any AAD but amiodarone.

Costs related to the index hospitalization include all health costs incurred by the healthcare payer, i.e. patient and government.

Results

Out of 1030 patients who underwent a catheter ablation of AF between November 2007 and the end of 2008, it was the first such procedure in 830. Follow-up extended from 24 to 38 months with a mean of 30.2 months. Mean (median) age was 58 (59) years and 597 (71.9%) of patients were men. About 77% were treated for paroxysmal and 23% for non-paroxysmal AF.

Two hundred and fourteen patients (25.8%) underwent one or more repeat ablations. Of these, there were 182 patients with one redo, 30 patients with two redos, 1 patient with three redos and 1 patient with four redos; 134 got their first redo within 1 year (16.1%) and 192 within 2 years (23.1%) (Table 1, model 1). The average number of ablations per patient was 1.3 over 30.2 months.

An electric cardioversion was performed in 218 patients (26.3%) during the follow-up period. It was performed at a mean of 220 (median 118) days after the index ablation. During the first year, 94 patients (11.3%) had a cardioversion beyond the blanking period. After 2 years, this number was 145 (17.5%) (Table 1, model 2).

The use of specific AADs and rate control drugs before and after the index procedure is depicted in Table 2.

Between 3 and 12 months after the procedure, 54.9% of patients were using at least temporarily an AAD. Between 3 and 24 months, this was 60.7% (Table 1, model 3a).

An AAD was started after a drug-free window of 1 month beyond the blanking period in 25.4 and 38.0% of patients within 1 and 2 years, respectively (Table 1, model 3c). A non-amiodarone AAD under those conditions was started in 35.7 and 46.5% after 1 and 2 years, respectively (Table 1, model 3b).

The combination of the occurrence of a repeat ablation, the need for electric conversion and the use of an AAD results in an estimate of failure of the index ablation of 59.8 and 65.9% after 1 and 2 years, respectively (Table 1, model 4a). If AAD use is counted as a failure only if the drug is started after an AAD-free month beyond the blanking period, AF recurrence estimates are 37.3 and 49.9% after 12 and 24 months, respectively (Table 1, model 4c). The scenario in-between, where any amiodarone use beyond the blanking period is considered a failure, leads to recurrence of AF estimates in 45.5 and 55.9% of patients after 12
and 24 months (Table 1, model 4b). The estimates of AF recurrence over time according these three models are depicted in the Kaplan–Meier plot shown in Figure 1.

We did not observe a relationship between a patient’s age or risk profile and the rate of recurrence of AF (data not shown).

Between 1 January 2006 until the day of the index ablation, 667 (80.4%) patients used an AAD and 718 (86.5%) a rate control drug (Table 2). Sotalol was used by 336 (40.5%) and amiodarone by 317 (38.2%) patients. Six hundred ninety-nine (84.2%) patients were at least temporarily treated with amiodarone, or sotalol, or a combination of an AAD (except amiodarone) and a rate control drug (except sotalol), indicating that up to 15.8% of patients might have undergone catheter ablation as a first-line therapy for their AF.

The cost for a catheter ablation of AF from the perspective of the healthcare payer on average amounted to about €9600 for the initial intervention. The upper limit of the yearly cost of a treatment of atrial fibrillation with a combination of a rate and a rhythm control drug in Belgium is about €300 per year.2

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### Table 1 Alternative models for the estimation of AF recurrence after a single catheter ablation

<table>
<thead>
<tr>
<th>Event</th>
<th>Model</th>
<th>Event</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>Repeat ablation</td>
<td>1</td>
<td>At least 1 repeat catheter ablation</td>
<td>134 16.1</td>
<td>192 23.1</td>
</tr>
<tr>
<td>Electric cardioversion</td>
<td>2</td>
<td>At least 1 electric cardioversion beyond blanking period</td>
<td>94 11.3</td>
<td>145 17.5</td>
</tr>
<tr>
<td>AAD use</td>
<td>3a</td>
<td>At least one AAD delivery beyond the blanking period</td>
<td>456 54.9</td>
<td>504 60.7</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>At least one delivery of one AAD over 9/21 months beyond a 3 months blanking period, taking into account that for non-amiodarone AADs an AAD-free window of 1 month beyond the blanking period is considered</td>
<td>296 35.7</td>
<td>386 46.5</td>
</tr>
<tr>
<td></td>
<td>3c</td>
<td>At least one delivery of one AAD over 9/21 months beyond a 3 months blanking period, taking into account an AAD-free window of 1 month beyond the blanking period</td>
<td>211 25.4</td>
<td>315 38.0</td>
</tr>
<tr>
<td>Combinations</td>
<td>4a</td>
<td>SUM (1 or 2 or 3a)</td>
<td>496 59.8</td>
<td>547 65.9</td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>SUM (1 or 2 or 3b)</td>
<td>378 45.5</td>
<td>464 55.9</td>
</tr>
<tr>
<td></td>
<td>4c</td>
<td>SUM(1 or 2 or 3c)</td>
<td>310 37.3</td>
<td>414 49.9</td>
</tr>
</tbody>
</table>

Total number of patients: 830. Follow-up is 12/24 months for repeat ablations, and 9/21 months (starting at the end of the 3 months blanking period) for electric cardioversion and AAD use.

### Table 2 Drug use before and after the index procedure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Before index ablation</th>
<th>1 year follow-up (3–12 months)</th>
<th>2 years follow-up (3–24 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n % (n = 830)</td>
<td>n % (n = 830)</td>
<td>n % (n = 830)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>317 38.2</td>
<td>126 15.2</td>
<td>165 19.9</td>
</tr>
<tr>
<td>Cibenzoline</td>
<td>56 6.7</td>
<td>25 3.0</td>
<td>26 3.1</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>9 1.1</td>
<td>1 0.1</td>
<td>2 0.2</td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>464 55.9</td>
<td>318 38.3</td>
<td>350 42.2</td>
</tr>
<tr>
<td>Propafenone</td>
<td>93 11.2</td>
<td>27 3.3</td>
<td>33 4.0</td>
</tr>
<tr>
<td>Quinidine</td>
<td>1 0.1</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Total AAD (class I and III)</td>
<td>667 80.4</td>
<td>456 54.9</td>
<td>504 60.7</td>
</tr>
<tr>
<td>Any beta-blocker</td>
<td>683 82.3</td>
<td>530 63.9</td>
<td>580 69.9</td>
</tr>
<tr>
<td>Verapamil</td>
<td>54 6.5</td>
<td>36 4.3</td>
<td>48 5.8</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>67 8.1</td>
<td>35 4.2</td>
<td>45 5.4</td>
</tr>
<tr>
<td>Digitalis glycosides</td>
<td>115 13.9</td>
<td>39 4.7</td>
<td>57 6.9</td>
</tr>
<tr>
<td>Total rate control drugs</td>
<td>718 86.5</td>
<td>564 68.0</td>
<td>613 73.9</td>
</tr>
</tbody>
</table>

Total number (%) of patients refers to patients who were prescribed at least one drug from the corresponding category. Sotalol is included in ‘Any beta-blocker’ and not in the ‘Total AAD’ count.
Discussion

So far, 10 randomized controlled trials (RCTs) have been published that test the effectiveness of catheter ablation of AF vs. drug treatment.\(^5–14\) In all but one\(^8\) the drug comparator consisted of a rhythm control drug. AF recurrence in those trials varies from 11.0% to 50.0%\(^8,11\), mostly after 1 year. Pooling of the efficacy results of the RCTs to obtain a single efficacy estimate is not straightforward. The inclusion criteria widely differ across trials and furthermore they show major methodological differences.\(^1\) Four trials predominantly enrolled paroxysmal AF patients,\(^6,10,12,13\) three studies were limited to patients with non-paroxysmal AF,\(^5,8,9\) and two other studies enrolled a mixed population.\(^7,11\) One trial compared a combination of catheter ablation and amiodarone with amiodarone only.\(^11\) One trial studied patients with diabetes mellitus only.\(^5\) Procedural success was defined by a single ablation procedure in some studies,\(^6,9,10\) while in others additional ablation attempts or re-initiation of AADs were allowed in determination of success. Cross over between study arms was widespread. In one study, catheter ablation was studied as first-line treatment for AF,\(^12\) whereas in the other studies patients were only eligible if they had failed at least one trial with an AAD.

Longer-term effects of catheter ablation up to 5 years are available from observational studies only. These also show a marked variation in the reported success. When looking at the larger studies of patients with paroxysmal AF, recurrence rates vary from 22 to 53% within 5 years after a single ablation, off-AAD. In patients treated for non-paroxysmal AF, this figure ranges between 33 and 71%.\(^2\)

The ablation procedure itself is not devoid of risks. Mortality rates up to 2.4 per thousand have been reported.\(^2\) Serious, life-threatening complications such as cardiac tamponade or stroke occur in 1–3% of the cases.\(^15,16\) An overall incidence of complications of 7.7% has been reported in a recent real-world multicentre survey.\(^17\) Added to this is the substantial exposure to radiation, estimated to be equivalent to 50–1350 chest X-rays, with a risk of cancer death of 0.2–2.1 per thousand ablations.\(^18\)

Based on administrative data, we sought to estimate the effectiveness of catheter ablation in patients that underwent a first catheter ablation for AF in Belgium. We considered any redo ablation a failure of the index procedure, assuming that an electrophysiologist would not go for a second procedure if he were not convinced that the first intervention was unsuccessful. Furthermore, we considered the index procedure having failed if a patient underwent an

Figure 1 Kaplan–Meier curves of time to protocol defined treatment failure. Atrial fibrillation recurrence over time according to models a, b, and c (Table 1). Time expressed in days, time 0 corresponding to the day of the index ablation.
electric cardioversion or was prescribed an AAD beyond the blanking period. This is in agreement with the definitions for use when reporting outcomes of AF ablation' proclaimed by the 2012 Consensus Statement on catheter ablation of AF. This concept, however, has not been thoroughly studied. Randomized controlled trials used a variety of definitions of short-term success such as freedom from symptomatic AF, freedom from symptomatic and asymptomatic episodes of AF, a >90% reduction of AF burden, the proportion of patients free of AF in a given period of time or on an ECG or Holter monitoring. For the time being, it is not clear whether partial success is a meaningful concept, however, has not been thoroughly studied. Randomized controlled trials used a variety of definitions of short-term success such as freedom from symptomatic AF, freedom from symptomatic and asymptomatic episodes of AF, a >90% reduction of AF burden, the proportion of patients free of AF in a given period of time or on an ECG or Holter monitoring. For the time being, it is not clear whether partial success is a meaningful outcome. Besides, there are no data on the long-term outcome of a partially successful ablation. A recent survey has shown that over a third of patients go for catheter ablation because of their desire for a drug-free lifestyle, indicating they would not consider the procedure a success if they need to continue an AAD.

The safety of AADs may be another argument in the pursuit of an AAD-free treatment. The superiority of rhythm control with AADs over rate control to improve quality of life could not be documented in clinical trials. This has been explained by some experts by the potentially serious side effects of AADs annihilating their presumed benefit on rhythm control. Of note, no single trial has compared catheter ablation with rate control in paroxysmal AF. It has also been argued that the continued use of AADs as such may not reliably reflect failure of an ablation since both physicians and patients may be reluctant to stop AADs to evaluate the clinical effectiveness of the ablation. Therefore, we considered an additional model to estimate recurrence rates in which an ablation was counted having failed only if an AAD was started after a drug-free period of at least 1 month beyond the blanking period. This resulted in estimates of AF recurrence of 37.3 and 49.9% after 1 and 2 years, respectively (Table 1, model 4c). In a model where the additional drug-free month was not applied to amiodarone, these estimates were 45.5 and 55.9%, respectively (Table 1, model 4b).

Although these results may be received as disappointing, they are located within the wide bounds of the off-AAD effectiveness of a single catheter ablation as reported in other observational studies.

The AF recurrences resulting from our analysis may be an underestimation of the actual recurrence rate. We may have missed patients in whom the procedure failed but the arrhythmia was simply accepted and no longer treated with AADs, cardioversion, or a repeat catheter ablation. The continued use of rate control drugs was not counted as a failure of the ablation, since these drugs are used for a variety of clinical conditions.

From our analysis of Belgian data, we conclude that up to 15.8% of patients may have undergone catheter ablation as a first-line treatment of AF. This figure is probably somewhat overestimated since we had no data available on drug use before 2006. According to recent guidelines, catheter ablation is a reasonable option as first-line therapy of paroxysmal AF. This approach has been studied in three RCTs so far. In a 2005 study, symptomatic AF recurred in 13% of patients after catheter ablation and in 63% of those who received an AAD. More recently, in the MANTRA-PAF trial (Medical Anti-Arrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation), the cumulative AF burden over 2 years, which was the primary endpoint of the study, was not significantly different among patients treated with drugs vs. those treated with catheter ablation. There was no difference in AF burden between the two study groups at 3, 6, 12, and 18 months. Only after 2 years, the difference was significant in favour of catheter ablation. In the RAAFT-2 trial (radiofrequency ablation vs. antiarrhythmic drugs as First-line treatment of symptomatic atrial fibrillation), patients who underwent catheter ablation had a significantly lower risk of a first recurrence of atrial tachyarrhythmia over 21 months (55% vs. 72%; HR 0.56, 95% CI: 0.35 to 0.90, P = 0.02) representing the primary efficacy endpoint of the study. However, focusing solely on events identified clinically eliminated the significant difference between the two groups (24% with catheter ablation vs. 31% with drug therapy; HR 0.86, 95% CI 0.42 to 1.72, P = 0.66). These two recent trials show that at least the short-term beneficial effect of catheter ablation as a first-line treatment is hardly better than an initial treatment with an AAD. Therefore, we feel that the use of catheter ablation as a first-line treatment of AF is not supported by conclusive evidence. Furthermore, from a health-economic point of view, it is hard to defend an expense of almost €10,000 for an intervention if a much cheaper alternative treatment with drugs is not considered first.

One of the aims of the health technology assessment from which this paper is extracted, was to also assess the cost-effectiveness of catheter ablation of AF. However, the lack of hard data on the procedure’s impact on endpoints such as quality of life, mortality, and stroke precludes a reliable cost-effectiveness assessment. What we do know is that AF recurrences after catheter ablation are common, that the procedure is associated with non-negligible complications and that it has a high initial cost. Therefore, we feel that catheter ablation should currently be strictly limited to symptomatic patients that are refractory to both rhythm and rate control, and in whom catheter ablation is currently believed to be most effective, i.e. those with paroxysmal AF and no or minimal structural heart disease. It has recently been argued that a more targeted selection of patients, based on the underlying pathophysiological mechanism of the AF, may lead to better results of catheter ablation.

**Conclusion**

We estimate that after 2 years follow-up, AF recurred off-AAD in 50% of Belgian patients who underwent a first catheter ablation in 2008. This estimation is based on counting redo ablations, the need for electric cardioversion and the need for the re-initiation of an AAD after a drug-free interval.

Our study has a number of limitations since data are based on administrative data and do not include clinical patient characteristics. Furthermore, they are derived from a nationwide experience, encompassing a broad range of ablation techniques, and including
both centres of excellence as well as less-experienced centres. The impact of these elements on outcomes could not be determined. However, our estimate of AF recurrence is in line with results from other observational studies.

The data suggest that the effectiveness of catheter ablation of AF in everyday practice may be lower than what one would expect from randomized trials. Therefore, and given the high initial cost in everyday practice may be lower than what one would expect from randomized trials. Therefore, and given the high initial cost, we recommend to strictly limiting the intervention to patients in whom it is currently believed to be most beneficial, i.e. those with severely symptomatic and drug-refractory paroxysmal AF with no or minimal structural heart disease. Further research is needed to better define AF patient subgroups that may benefit most from catheter ablation.

Conflict of interest: none declared.

References