Temporal changes in patient characteristics and prior pharmacotherapy in patients undergoing radiofrequency ablation of atrial fibrillation: a Danish nationwide cohort study

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Received 24 July 2012; accepted after revision 29 November 2012; online publish-ahead-of-print 2 January 2013

Aims

Trends in patient selection and pharmacotherapy before radiofrequency ablation (RFA) of atrial fibrillation are not well studied. We examined temporal trends in RFA utilization on a nationwide scale in Denmark.

Methods and results

Using the cross-linkage of nationwide registers, 3302 atrial fibrillation patients treated with ‘first-ever’ RFA between 2000 and 2009 were identified. Median age was 59 years (interquartile range 53–65) and 73.8% were males. From 2000–01 to 2008–09 the median age increased from 55 (48–61) to 61 (55–66) years (P < 0.0001). The proportion of patients with hypertension and diabetes mellitus increased from 34.8 to 50.6% (P < 0.0001) and 2.2 to 5.9% (P < 0.01), respectively. The proportion of patients with heart failure, vascular disease or previous stroke remained unchanged. The percentage of patients with CHA2DS2-VASc score ≥ 2 increased from 23.9 to 41.5% (P < 0.0001). The proportion of patients who did not receive any class Ic or class III antiarrhythmic drugs (AADs) within 2 years prior to ‘first-ever’ RFA increased from 8.7 to 22.7% (P < 0.0001). Prior use of sotalol and class Ic AADs decreased from 63 to 6.3% (P < 0.0001) and from 35 to 24% (P < 0.0001), respectively. Amiodarone and beta-blockers prior to RFA were used in 36 and 82% of all patients, respectively, without significant temporal changes.

Conclusion

During a 10-year period, RFA was increasingly performed in older patients with higher co-morbidity, and without prior trial of antiarrhythmic therapy. These findings may provide a framework to understand the outcomes of RFA.

Keywords

Radiofrequency ablation • Atrial fibrillation • Temporal changes • Patient characteristics • Pharmacotherapy • Antiarrhythmic drugs

Introduction

Radiofrequency catheter ablation (RFA) has emerged over the past decade as a reasonable treatment option for recurrent symptomatic atrial fibrillation (AF). Initially, RFA was mainly performed on symptomatic patients with drug refractory paroxysmal AF, excluding those with underlying structural heart disease.1,2 Indications were expanded in 2006 when the updated AF guidelines from American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) suggested RFA as the second-line therapy to maintain sinus rhythm in symptomatic patients with coronary artery disease, heart failure, or hypertension, in addition to persistent AF.3,4 In 2010, ESC guidelines for the management of AF advised RFA regardless of AF subtype or patient substrate, when patients remain symptomatic despite adequate medication with antiarrhythmic drugs (AADs).3 According to the current focused update of ESC guidelines,6 RFA should be considered as the first-line therapy for rhythm control without trial of AADs in selected symptomatic patients with paroxysmal AF and low risk for procedural complications.

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RFA is now commonly used to treat symptomatic AF. However, little is known about how trends in patient selection and prior pharmacotherapy have changed in the contemporary era of RFA. Attaining this knowledge would contribute to better understanding of treatment outcomes. We therefore described temporal changes in the use of RFA procedures and prior pharmacotherapy in patients with AF undergoing RFA in Denmark between 2000 and 2009.

Methods

Databases

Every hospital admission in Denmark has been recorded in the Danish National Patient Registry since 1977.7 Admissions are coded with one primary and, if appropriate, one or more secondary diagnoses at discharge, according to the International Classification of Diseases; the 8th revision (ICD-8) until 1994, and the 10th revision (ICD-10) since 1994. All RFA procedures have been registered in the Danish National Patient Registry, and coded according to the Danish healthcare system classification of treatment procedures (SKS), which has been developed and maintained by the Danish National Board of Health since 1992 (obtained from http://medinfo.dk/sks; 6 November 2012, date last accessed).

The Danish Registry of Medicinal Product Statistics keeps records of all prescriptions according to the Anatomical Therapeutic Chemical (ATC) classification system since 1995. This registry retains accurate information on date of dispensing, quantity, strength, and affiliation of the physician issuing the prescription.8,9 All residents in Denmark have a unique identification number that enables cross-linkage of data from nationwide registers on an individual level.

Study population

From the Danish National Patient Registry, we identified all patients with AF who underwent RFA in Denmark between 1 January 2000 and 31 December 2009. We included only patients aged 18 years or older, with a ‘first-ever’ RFA (SKS: BFFB04) plus a previous diagnosis of AF (ICD-10: I48). For each patient, the Danish National Patient Registry was screened for previous hospitalizations for AF, commencing from January 1995. Patients without data on sex, date of birth, and previous AF diagnosis were excluded. Atrial fibrillation duration was defined as the time from ‘first-ever’ hospitalization for AF to ‘first-ever’ RFA. The population was divided in five ‘2-year’ strata according to the year of RFA to evaluate the temporal changes.

Identification of the population was validated by cross-checking the nationwide database with a local database from Copenhagen University Hospital Gentofte, one of the six cardiac centres performing RFA in Denmark. The local database was systematically updated since 2004. Patients were matched by unique identification number and the date of ‘first-ever’ RFA. During the period 509 patients underwent RFA at Copenhagen University Hospital Gentofte, of which 492 patients could be identified from the nationwide database, yielding 97% sensitivity.

Co-morbidity

Heart failure was defined as combination of previous heart failure diagnosis and use of loop-diuretics as previously described.10 Drug-treated hypertension was defined as the use of two different anti-hypertensive drugs, which has a positive predictive value of 80.0% and specificity of 94.7%.11 Drug-treated diabetes mellitus was defined as the use of glucose-lowering medication. Previous stroke including transient ischaemic attack and vascular disease (peripheral artery disease or coronary heart disease) were identified from the Danish National Patient Registry, as previously described.12–14 The Appendix shows the identification of these co-morbidities in detail.

Thromboembolic risk assessment

As recommended by the current European guidelines4 thromboembolic risk was estimated according to CHA2DS2-VASc score, a risk stratification scheme with maximum score of 9. This score is calculated by adding one point each for the presence of heart failure, hypertension, diabetes mellitus, vascular disease, age 65–74 years, and female sex category, whereas previous stroke or age ≥75 years receives two points.11,15

Pharmacotherapy

Pharmacotherapy, received within 2 years prior to ‘first-ever’ RFA, was identified from the Danish Registry of Medicinal Product Statistics and classified into three groups: (i) AADs: amiodarone (C01BD01), sotalol (C07AA07) and flecainide (C01BC04). (ii) Rate control drugs: beta-blockers (C07) excluding sotalol, digoxin (C01A), and non-diuretic diuretics calcium antagonists (verapamil and diltiazem (C08D)). (iii) Oral anticoagulants (OAC): warfarin (B01AA03) and phenprocoumon (B01AA04).

Statistical analysis

Results for continuous variables were given as median values with interquartile range (IQR) or as means with standard deviation (SD), and differences were calculated by Kruskal–Wallis test. Temporal differences in categorical variables were assessed by χ² test. A two-sided significance level of 0.05 was used in comparisons. Multivariable logistic regression models were applied to identify covariates associated with use of AADs. The models were adjusted for age (<45 years as reference), sex (women as reference), hypertension, heart failure, and coronary heart disease (absence of co-morbidities as reference). Regarding only amiodarone, we adjusted the models also for prior use of sotalol and class 1c AADs to assess the effect of early use of these AADs on later use of amiodarone. All statistical calculations were performed using the SAS statistical software package, version 9.2 (SAS Institute Inc.).

Ethics

The Danish Data Protection Agency has approved the present study (Ref. 2007-58-0015, int. ref: GEH-2010-001). Individual data used in the present study were encrypted and made accessible to us so that individuals could not be identified. Retrospective register-based studies do not require ethical approval according to Danish regulations.
Results

Population
We identified 3374 patients with AF undergoing RFA between 2000 and 2009. After excluding 28 patients without data on birthday or sex, and 44 patients lacking prior diagnosis of AF, the final study population consisted of 3302 individuals.

Table 1 shows the baseline patient characteristics. The median age was 59 years (IQR 53–65), increasing substantially from 55 years (IQR 48–61) in 2000–01 to 61 years (IQR 55–66) in 2008–09 (P < 0.0001). Most of the patients were male (73.8%), and there were no significant temporal changes in the sex distribution. The number of patients undergoing RFA increased markedly during the period from 46 in 2000–01 to 1388 in 2008–09 (Figure 1).

Co-morbidity and thromboembolic risk
Radiofrequency ablation was increasingly performed in patients with higher co-morbidity. The most prevalent co-morbidity was hypertension (45%), and the percentage of patients with hypertension and diabetes mellitus increased significantly (Table 1). Heart failure, vascular disease, or previous stroke was identified in 3–8% of patients, without significant temporal evolutions. The percentage of patients with CHA2DS2-VASc score ≥ 2 increased from 23.9% in 2000–01 to 41.5% in 2008–09 (P < 0.0001), whereas patients with CHA2DS2-VASc score of 0 decreased from 39.1 to 26.4% (P < 0.0001).

Pharmacotherapy
Number of AADs used per patient decreased over time (Table 1). The percentage of patients who did not receive any AADs within the last 2 years prior to ‘first-ever’ RFA increased significantly from 8.7% in 2000–01 to 22.7% in 2008–09 (Figure 2A). The use of sotalol represented the most prominent change, showing a 10-fold decrease from 63% in 2000–01 to 6.3% in 2008–09, whereas the percentage of patients receiving class Ic AADs decreased from 35 to 24% (Figure 2B). An average of 36% of the patients used amiodarone, without significant changes during the period. The total number of AADs used prior to ‘first-ever’ RFA decreased from an average of 1.5 in 2000–01 to 0.7 in 2008–09 (P < 0.0001).

Figure 3 depicts the multivariable logistic regression analysis applied to identify covariates associated with the use of AADs. Class Ic AADs was used less in patients with hypertension, heart failure, and coronary heart disease. Presence of hypertension and heart failure was associated with less use of sotalol, and more use of amiodarone. Use of amiodarone was also strongly associated with previous use of sotalol and class Ic AADs. No sex-related differences were observed in the use of AADs. The age had no effect on the use of sotalol and class Ic AADs, while increasing age was associated with higher use of amiodarone, except for patients older than 75 years. These results were consistent in multivariable analyses.

Figure 4 illustrates evolutions in the use of OAC and rate control drugs. Use of OAC increased from 65.2% in 2000–01 to a plateau at 98% after 2004–05 irrespective of estimated thromboembolic risk. In total, 95, 95.9, and 96.7% of patients with

Table 1 Baseline characteristics

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</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>3302 (100)</td>
<td>46 (1.4)</td>
<td>207 (6.3)</td>
<td>546 (16.5)</td>
<td>1115 (33.7)</td>
<td>1388 (42)</td>
</tr>
<tr>
<td>Median age in years (IQR)</td>
<td>59 (53–65)</td>
<td>55 (48–61)</td>
<td>56 (49–61)</td>
<td>58 (52–64)</td>
<td>60 (54–65)</td>
<td>61 (55–66)</td>
</tr>
<tr>
<td>Age 65–74, n (%)</td>
<td>784 (23.7)</td>
<td>5 (10.9)</td>
<td>35 (16.9)</td>
<td>100 (18.3)</td>
<td>273 (24.5)</td>
<td>371 (26.7)</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>864 (26.2)</td>
<td>11 (23.9)</td>
<td>44 (21.3)</td>
<td>132 (24.2)</td>
<td>298 (26.7)</td>
<td>379 (27.3)</td>
</tr>
<tr>
<td>AF duration in years (IQR)</td>
<td>3.1 (1.3–6.5)</td>
<td>2.2 (1.1–4.2)</td>
<td>2.9 (1.2–5.4)</td>
<td>3.8 (1.3–6.8)</td>
<td>3.2 (1.1–6.4)</td>
<td>3.1 (1.3–6.7)</td>
</tr>
<tr>
<td>Number of prior AADs (SD)</td>
<td>0.9 (0.7)</td>
<td>1.5 (0.9)</td>
<td>1.4 (0.8)</td>
<td>1.1 (0.8)</td>
<td>0.8 (0.7)</td>
<td>0.7 (0.6)</td>
</tr>
<tr>
<td>Co-morbidity, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>1485 (45)</td>
<td>16 (34.8)</td>
<td>61 (29.5)</td>
<td>211 (38.6)</td>
<td>494 (44.3)</td>
<td>703 (50.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>154 (4.6)</td>
<td>1 (2.2)</td>
<td>3 (1.4)</td>
<td>18 (3.3)</td>
<td>50 (4.5)</td>
<td>82 (5.9)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>204 (6.2)</td>
<td>3 (6.5)</td>
<td>6 (2.9)</td>
<td>34 (6.2)</td>
<td>75 (6.7)</td>
<td>86 (6.2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>220 (6.6)</td>
<td>2 (4.3)</td>
<td>12 (5.8)</td>
<td>43 (7.9)</td>
<td>78 (7.0)</td>
<td>85 (6.1)</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td>200 (6.1)</td>
<td>3 (6.5)</td>
<td>11 (5.3)</td>
<td>30 (5.5)</td>
<td>63 (5.7)</td>
<td>93 (6.7)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>176 (5.3)</td>
<td>1 (2.2)</td>
<td>10 (4.8)</td>
<td>26 (4.8)</td>
<td>56 (5.0)</td>
<td>83 (6.0)</td>
</tr>
<tr>
<td>Periphery artery disease</td>
<td>30 (0.9)</td>
<td>2 (4.4)</td>
<td>2 (1.0)</td>
<td>5 (0.9)</td>
<td>8 (0.7)</td>
<td>13 (0.9)</td>
</tr>
<tr>
<td>CHA2DS2-VASc score, n (%)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Score = 0</td>
<td>1009 (30.5)</td>
<td>18 (39.1)</td>
<td>90 (43.4)</td>
<td>195 (35.7)</td>
<td>340 (30.5)</td>
<td>366 (26.4)</td>
</tr>
<tr>
<td>Score = 1</td>
<td>1051 (31.8)</td>
<td>17 (37.0)</td>
<td>73 (35.3)</td>
<td>161 (29.5)</td>
<td>354 (31.7)</td>
<td>446 (32.1)</td>
</tr>
<tr>
<td>Score ≥ 2</td>
<td>1242 (37.6)</td>
<td>11 (23.9)</td>
<td>44 (21.3)</td>
<td>190 (34.8)</td>
<td>421 (37.8)</td>
<td>576 (41.5)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; AADs, antiarrhythmic drugs; SD, standard deviation.
Discussion

This study has three main findings: (i) there has been a major increase in use of RFA procedures for the treatment of AF, (ii) RFA was increasingly performed in older patients with higher co-morbidity, and (iii) the proportion of patients undergoing ‘first-ever’ RFA without prior trial of AAD therapy has increased substantially.

Since the past decade RFA has become a feasible option for the treatment of AF due to evolving techniques, improved safety, and promising short-term outcomes. While the long-term benefit of RFA remains controversial, worldwide expansion of RFA utilization has resulted in widened indications and increased willingness to treat more patients with coexisting cardiovascular conditions, leading to changing patterns of patient selection.

Increasing age may reflect the widened indications for patients undergoing RFA, and was previously addressed by an older single-centre study. While some studies conclude that advanced age has no prominent effect on outcomes of RFA, one study reports that age is an independent predictor of late AF recurrence. Increasing age could also explain the increasing rate of hypertension and diabetes mellitus, and these changes in patient characteristics may influence the efficacy outcomes of RFA. Berreuzo et al. investigated AF recurrence following RFA in 148 consecutive patients and found that hypertension was an independent predictor along with left atrial diameter. Chao et al. studied atrial substrate properties and AF recurrence rate after RFA in 228 patients with paroxysmal AF and abnormal glucose metabolism, i.e. impaired fasting glucose or diabetes mellitus. They found intra-atrial conduction delay, decreased voltage, and higher AF recurrence rate over an average of 18.8 months of follow-up in patients with abnormal glucose metabolism compared with those without. Although technology, technique, and experience with RFA have been improving, increasing co-morbidity and age may thus provide an explanation for stagnant success rates following RFA.

The average number of AADs used per patient prior to RFA decreased significantly as previously suggested, reflecting reduced the intensity of antiarrhythmic pharmacotherapy before RFA. We also observed a substantial increase in patients undergoing RFA without using any AADs (Figure 2A), highlighting an increasing trend for using RFA as a first-line therapy. This treatment pattern may indicate a discrepancy between real-life treatment practice and the applicable international guidelines of the period that recommended trial of at least one AAD to prevent symptomatic AF recurrences before referring patients to RFA. Nonetheless, our registry data do not allow us to determine the underlying reason(s). It is possible that some patients tried and failed AADs during admission and therefore never had the AADs prescribed, or AADs were not used due to patient or physician preference for ablation. A recent single-centre study reports that the motive for not taking AADs before RFA was patient’s preference in 71%, and contraindications to AADs in 29%. It cannot be ruled out that financial incentives and/or competition between expanding centers may have played a role. Moreover, 90 patients not receiving AADs in the period were randomized in Denmark to RFA-arm (n = 146) in international MANTRA-PAF trial (The Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation).
Radiofrequency ablation was also advocated as first-line therapy in expert opinion papers in this period that emphasized the safety and efficacy of RFA, the advantage of sustaining sinus rhythm as well as severe adverse effects, poor efficacy, and increased mortality associated with AADs. Recently, MANTRA-PAF trial compared RFA with AADs as first-line therapy on an intention-to-treat basis over a 24-month follow-up. Although total AF burden did not differ remarkably, significantly more patients in the RFA-arm were free from any AF and symptomatic AF at 24 months, and quality of life was significantly better in the RFA-arm at 12 and 24 months. RAAFT-II trial (Radiofrequency Ablation for Atrial Fibrillation Trial) along with other randomized and non-randomized studies provided similar findings. According to the current ESC guidelines, (i) RFA of symptomatic paroxysmal AF is now recommended for patients experiencing symptomatic AF recurrences on AADs (Class I indication, Level of evidence A), and (ii) RFA should be considered as first-line therapy for patients with paroxysmal AF and low complication risk for RFA procedure (Class IIa indication, Level of evidence B).

Although left ventricular hypertrophy was not included in our multivariable analyses, patterns in the use of AADs prior to RFA in Denmark (Figure 3) seem to be consistent with international
guidelines. Substantial reduction in the use of class Ic AADs and sotalol (Figure 2B) is also in line with nationwide trends in treatment of AF.31 Although adverse effects of amiodarone are well known, it is currently the most efficient AAD to prevent the recurrences of AF.32,33 Congruently, amiodarone was recommended as second-line therapy when class Ic AADs or sotalol fails, suggesting a possible explanation for consistency in the use of amiodarone.

We observed increasing use of OAC early in the period and very prevalent use of OAC, irrespective of thromboembolic risk estimated by CHA2DS2-VASc score. This was probably due to increased awareness about risk of stroke reported during the period,34–36 which resulted in a general consensus in Denmark for initiating 3–4 week oral anticoagulation prior to RFA. Due to lack of data on AF nature, the extent to which AF nature was responsible for prevalent use of OAC in low-risk patients is also unclear. Furthermore, several papers have previously demonstrated no correlation between CHADS2-score and initiation of anticoagulation in patients with AF.11,37 Declining use of rate-control drugs seems to mimic nationwide trends,31 except that the use of beta-blockers is quite prevalent and stationary.

Limitations and strengths
Precise indications for RFA, frequency of AF episodes, and the nature of AF (paroxysmal vs. persistent) were not available, as this study was based on administrative registries that do not cover echocardiographic variables or clinical data. Especially lack of echocardiographic data and data on nature of AF might have a significant effect on the use of AADs, rate-control drugs, and anticoagulant therapy. Although it is conceivable that some of the patients were referred to RFA without prior hospitalization, we did not have access to data on patients treated by general practitioner or private practicing cardiologist, restricting the accuracy of AF duration estimates. Absence of data on blood pressure measurements and fasting blood glucose levels might have led to the exclusion of individuals with undiagnosed hypertension, undiagnosed diabetes mellitus or impaired fasting glucose at baseline.

While the epidemiological approach has these limitations, the registries used for this study comprise all patients regardless of participation in the labour market, and are not affected by selection bias caused by including selected hospitals, certain health insurance systems, or age groups. This study yields therefore data reflecting the ‘real-life’ clinical practice on a nationwide scale. Although there may be possible individual differences between countries in management strategies for AF, a comprehensive accumulation of nationwide data on hospitalizations and possibility of cross-linkage to other registries are unique for Denmark.

Conclusion
In the contemporary era of RFA, the expanded indications have substantially influenced patient characteristics, resulting in the treatment of older patients with a higher co-morbidity. Furthermore, despite the recommendation of prior trial of antiarrhythmic therapy before referral to RFA, increasing number of patients undergo RFA without any use of antiarrhythmic therapy. These findings may provide a framework to understand the outcomes of RFA.

Conflict of interest: none declared.

Funding
This work was supported by Danish Heart Foundation [grant number 12-04-R90-A3820-2271]; and FUKAP, research fund of The Department of Cardiology, Copenhagen University Hospital Gentofte where this work was executed. GHG is supported by an independent Research Scholarship from the Novo Nordisk Foundation.

Appendix: Definition of co-morbid conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>ICD-8 Codes</th>
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<tbody>
<tr>
<td>Heart failure</td>
<td>425, 4270–4271 or ICD-10: I110, H42, I50, J819 plus treatment with</td>
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<tr>
<td></td>
<td>loop-diuretics (ATC-code: C03C) and prescription claimed within 180 days</td>
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<tr>
<td></td>
<td>prior to ‘first-ever’ RFA procedure</td>
</tr>
<tr>
<td>Drug-treated hypertension</td>
<td>Patients receiving minimum two different kinds of anti-hypertensive medicine</td>
</tr>
<tr>
<td></td>
<td>(ATC-code: C) and prescriptions claimed within 180 days prior to ‘first-ever’</td>
</tr>
<tr>
<td></td>
<td>RFA procedure</td>
</tr>
<tr>
<td>Drug-treated diabetes</td>
<td>Treatment with glucose lowering drugs (ATC-code: A10) and prescription</td>
</tr>
<tr>
<td>mellitus</td>
<td>claimed within 180 days prior to ‘first-ever’ RFA procedure</td>
</tr>
<tr>
<td>Previous stroke or transient cerebral ischaemia</td>
<td>ICD-8: 433–438 or ICD-10: G458-G459, 163–164</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>Presence of</td>
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<td></td>
<td>Coronary heart disease (ICD-8: 410 or ICD-10: I21, I22) or</td>
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<tr>
<td></td>
<td>Periphery artery disease (ICD-8: 440, 444 or ICD-10: I170, I702-I709, I74)</td>
</tr>
</tbody>
</table>

Figure 4 The temporal evolvements in percentage of patients receiving oral anticoagulants and rate-control therapy prior to RFA by year. OAC, Oral anticoagulants; CCA, Non-dihydropyridine calcium antagonists.
Changes in patient characteristics and prior pharmacotherapy in patients undergoing RFA of AF

References


