Oral anticoagulation therapy after radiofrequency ablation of atrial fibrillation and the risk of thromboembolism and serious bleeding: long-term follow-up in nationwide cohort of Denmark

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Aim
To investigate the long-term risk of thromboembolism and serious bleeding associated with oral anticoagulation (OAC) therapy beyond 3 months after radiofrequency ablation (RFA) of atrial fibrillation (AF).

Methods and results
Linking Danish administrative registries, 4050 patients undergoing first-time RFA (2000–11) were identified. Risk of thromboembolism and serious bleeding according to OAC therapy were analysed by incidence rates (presented per 100 person-years) and Cox proportional-hazard models. The median age was 59.5 years (interquartile range, IQR: 52.8–65.2); 26.5% were females. During a median follow-up of 3.4 years (IQR: 2.0–5.6), 71 (1.8%) thromboembolism cases were identified, where incidence rates with and without OAC were 0.56 (0.40–0.78)95%CI and 0.64 (0.46–0.89)95%CI, respectively. Oral anticoagulation discontinuation remained insignificant [hazard ratio 1.42(0.86–2.35)95%CI] in multivariable analysis. Beyond 3 months after RFA 87 (2.1%) serious bleedings occurred; incidence rates with and without OAC were 0.99 (0.77–1.27)95%CI and 0.44 (0.29–0.65)95%CI, respectively. Oral anticoagulation therapy was significantly associated with serious bleeding risk [hazard ratio 2.05(1.25–3.35)95%CI]. In an age- and gender-matched cohort (1 : 4) of 15 848 non-ablated AF patients receiving rhythm-control therapy, thromboembolic rates with and without OAC were 1.34 (1.21–1.49)95%CI and 2.14 (1.98–2.30)95%CI, respectively. Adjusted incidence rate ratio was 0.53 (0.43–0.65)95%CI favouring RFA cohort.

Conclusion
Thromboembolic risk beyond 3 months after RFA was relatively low compared with a matched non-ablated AF cohort. With cautious interpretation due to low number of events, serious bleeding risk associated with OAC seems to outweigh the benefits of thromboembolic risk reduction. Randomized studies are warranted to test our results.

Keywords
Oral anticoagulation • Radiofrequency ablation • Atrial fibrillation • Risk • Thrombosis • Bleeding

Introduction
Radiofrequency ablation (RFA) is a recommended treatment for symptomatic drug-resistant atrial fibrillation (AF), while it remains uncertain whether RFA is associated with reduction in thromboembolic complications related to AF.1–3 European Society of Cardiology guidelines for the management of AF from 2010 recommended that systemic oral anticoagulation (OAC) should be sustained for minimum of 3 months after RFA, and further evaluation of persistent OAC therapy should be based on individual patients’ risk factors for stroke (Class of recommendation IIa, level of evidence C).1 Notably, OAC discontinuation after RFA was not recommended in patients at high risk of stroke.
The benefit of OAC therapy for thromboembolic risk reduction is believed to outweigh the measurable risk of bleeding in most AF patients. Nevertheless, the benefit of post-ablation OAC on thromboembolic risk is not fully elucidated, and there is need of further assessment in AF patients undergoing RFA, who are not included in current risk stratification schemes. The safety of OAC discontinuation beyond 3 months after RFA remains controversial, and little is known about the risk of serious bleeding associated with post-ablation OAC therapy. Improved knowledge of the risks and benefits of post-ablation OAC therapy will help to develop evidence-based OAC treatment strategies and reduce the incident thromboembolism and serious bleeding. We investigated the long-term risk of thromboembolism and serious bleeding according to post-ablation OAC therapy over a 5-year follow-up in a nationwide cohort of 4050 AF patients treated with RFA in Denmark between 2000 and 2011.

Methods

Data sources
The Danish National Patient Registry holds information on every hospital admission in Denmark since 1978. At discharge, hospitalizations are coded with one primary diagnosis and, if appropriate, one or more secondary diagnoses according to the International Classification of Diseases; the 10th revision (ICD-10) since 1994. All RFA procedures performed in public or private sector in Denmark have been registered and coded according to NOMESCO (The Nordic Medico-Statistical Committee) Classification of Surgical Procedures (NCSP). Since 1995, the Danish Registry of Medicinal Product Statistics has accurately kept records of all prescriptions dispensed from Danish pharmacies according to the Anatomical Therapeutic Chemical (ATC) classification system, including data on date, quantity, strength, formulation, and affiliation of the prescribing physician. The civil registration system holds data on age, sex, and vital status of patients where all deaths are registered within 14 days of occurrence. A unique and permanent civil registration number provided for each resident in Denmark enables cross-linkage between these nationwide administrative registries at the individual level.

Study population
From the Danish National Patient Registry, all patients with AF (ICD-10: I48) without previous mitral or aortic valve surgery (NCSP: KF1, KFM), aged 18 years or older, undergoing first-time RFA (NCSP: BFFB04) in Denmark (public or private) between 1 January 2000 and 31 December 2011 were identified and included from the discharge date following first-time RFA. Patients with missing data such as sex and date of birth were excluded (n = 252). This algorithm for identifying the AF patients undergoing first-time RFA was previously validated, yielding 97% sensitivity.

Post-ablation oral anticoagulation therapy
Oral anticoagulation therapy after discharge from first-time RFA was identified based on the number and strength of warfarin tablets (ATC: B01AA03) received at prescription claims divided by the number of days until next prescription claim. Average daily warfarin dosage and therapy duration was estimated using up to nine consecutive prescription periods. Oral anticoagulation therapy was assumed to be maintained until no residual warfarin tablets were available in patients’ possession. Oral anticoagulation discontinuation was defined as no available treatment according to estimated dosage. This algorithm allows for changes in exposure status and dosage over time. Sensitivity analyses were performed by lengthening of OAC treatment periods by 7, 14, and 21 days above calculated treatment duration. Quantification of average dose and therapy duration by this algorithm has been described and used previously. Aspirin treatment was managed correspondingly.

Comorbidity and pharmacotherapy
The definitions are detailed with corresponding codes in Supplementary material online, Table S1. These comorbidities were considered valid if the discharge diagnoses were registered within 5 years and the prescriptions were claimed within 180 days before inclusion. Heart failure was defined from previous discharge diagnosis combined with use of loop diuretics, as described previously. Using minimum two different types of anti-hypertensive medication was used to identify hypertension. Diabetes mellitus was identified from any use of glucose-lowering medication. Patients with previous stroke, vascular disease (i.e., peripheral arterial embolism and/or coronary artery disease), renal failure, liver disease, and alcohol abuse were identified from the Danish National Patient Registry. Previous serious bleeding was defined as hospitalization for intracranial bleeding, or bleeding from the respiratory, gastrointestinal, or urinary tract.

The following drugs were registered at baseline: warfarin, aspirin, clopidogrel, antiarrhythmic drugs (class Ic AADs, amiodarone, and sotalol), β-blockers, digoxin, verapamil, statins, and non-steroidal anti-inflammatory drugs.

Risk profile
Thromboembolic risk profile was estimated by the CHA2DS2-VASc score, a risk stratification scheme with maximum score of 9, estimated by counting two points each for previous stroke and aged ≥ 75 years, whereas heart failure, hypertension, diabetes, vascular disease, aged 65–74, and being female takes one point. Thromboembolic risk was considered low, intermediate, and high if CHA2DS2-VASc score was 0, 1, and ≥ 2, respectively.

Risk profile for serious bleeding was assessed by the HAS-BLED score obtained by adding one point each for hypertension, abnormal renal function, abnormal liver function, stroke, previous bleeding, elderly (aged > 65), drug consumption, and alcohol abuse. This score ranged 0–8 points since no information on labile international normalized ratio (INR) was available. The risk of serious bleeding was considered low, intermediate, and high if HAS-BLED score was ≤ 1, 2, and ≥ 3, respectively.

Recurrent atrial fibrillation
The earliest record of any hospitalization for AF with or without direct cardioversion (DC), or re-ablation procedure after the 3 months blanking period beyond first-time RFA was considered as recurrent AF, and treated as time-dependent covariate. The sensitivity, specificity, and positive predictive value of this definition of AF recurrence was 99.3, 95.2, and 98%, respectively (Supplementary material online, Section 4).

Outcome measures and follow-up
The definitions are detailed in Supplementary material online, Table S2. Primary outcome measure was thromboembolism defined as hospitalization for ischemic stroke, transient ischemic attack (TIA), or peripheral artery embolism. Ischemic stroke in the Danish National Patient Registry has a positive predictive value (PPV) of 97–100%, while PPV for unspecified stroke is 80.5–86%, and PPV for TIA is 57.9–68.4%. Secondary outcome measure was serious bleeding defined as hospitalization for intracranial bleeding, or bleeding from respiratory, gastrointestinal, or urinary tract. The definition, occurrence, and type of serious bleeding have a PPV of 89–99%.
Follow-up was commenced from 90 days after first-time RFA, and patients were followed until the first event, otherwise censored at death from another cause, or at the end of the 5-year period. Events occurring within 30 days after any re-ablation procedure were considered potentially procedure-related and also censored.

Statistical analysis
Continuous variables were reported as mean with SD or median with interquartile range (IQR) where differences were calculated by the Kruskal–Wallis test. Categorical variables were reported as numbers with percentages and differences were assessed by $\chi^2$-test. A two-sided significance level of 0.05 was used in evaluations. Event rates were calculated as number of new cases per 100 person-years. Events that occurred during the 3 months blanking period were reported with numbers and incidence rates, and were not included in the primary analyses. The present cohort was compared (1 : 4) with a non-ablated AF population receiving rhythm-control treatment (AADs or DC or both) in a propensity score-matched analysis, calculated by logistic regression conditional on age, sex, and year of inclusion. Thromboembolic rates were determined with and without use of OAC therapy. Adjusted incidence rate ratio (RFA vs. no-RFA) was estimated controlling for use of OAC, Aspirin, Clopidogrel, and the components of the CHA2DS2-VASc score. Fine-Gray competing risk regression was performed to illustrate confounders by univariate model at thromboembolism and serious bleeding after identification of potential models were performed to identify the predictors associated with recurrent AF as it was a time-dependent variable. Cox proportional-hazard models for cumulative incidences were constructed disregarding recur-
procedure-related events were considered competing events. The 5-year cumulative incidences, where death from another cause and incidence rates, were not included in the primary analyses. The present cohort was compared (1 : 4) with a non-ablated AF population receiving rhythm-control treatment (AADs or DC or both) in a propensity score-matched analysis, calculated by logistic regression conditional on age, sex, and year of inclusion. Thromboembolic rates were determined with and without use of OAC therapy. Adjusted incidence rate ratio (RFA vs. no-RFA) was estimated controlling for use of OAC, Aspirin, Clopidogrel, and the components of the CHA2DS2-VASc score. Fine-Gray competing risk regression was performed to illustrate the 5-year cumulative incidences, where death from another cause and procedure-related events were considered competing events. The models for cumulative incidences were constructed disregarding recurrent AF as it was a time-dependent variable. Cox proportional-hazard models were performed to identify the predictors associated with thromboembolism and serious bleeding after identification of potential confounders by univariate model at $P < 0.2$ and stratified analyses. The final multivariable model for thromboembolism was adjusted for OAC discontinuation (reference: OAC treatment), aspirin use, the components of CHA2DS2-VASc score, and recurrent AF. The final model for serious bleeding was adjusted for OAC therapy (reference: OAC discontinuation), aspirin use, and the components of HAS-BLED score. The CHA2DS2-VASc or HAS-BLED score of 0, no aspirin treatment, and no recurrent AF were reference in the models. Data management and statistical analyses were performed using the SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC, USA) and Stata statistical software, version 11.0 (Stata Corp LP, College Station, TX, USA).

Ethics
The Danish Data Protection Agency has approved the present study (Ref. 2007-58-0015, int. ref: GEH-2010-001). According to Danish regulations, register-based retrospective studies do not require ethical approval. Anonymised individual data were made accessible and used in this study so that individuals could not be identified. Statistical packages were arranged via encrypted servers by Statistics Denmark.

Results
Population
Final study population comprised 4050 patients undergoing first-time RFA. The median age was 59.5 years (IQR: 52.9–65.2); 73.5% were men. According to the CHA2DS2-VASc score, 1275 (31.5%) low-risk, 1268 (31.3%) intermediate-risk, and 1507 (37.2%) high-risk patients were identified. Median follow-up duration was 3.4 years (IQR: 2.0–5.6). Table 1 shows the baseline patient characteristics. After the 3 months blanking period, 2179 (53.8%) of patients had recurrent AF. Patients underwent a total of 5983 and a mean of 1.48 (SD 0.7) RFA procedures.

**Table 1** Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Median age (years) (IQR)</th>
<th>Aged 65–74</th>
<th>Aged ≥ 75</th>
<th>Female</th>
<th>AF duration (years) (IQR)</th>
<th>Mean number of prior AADs (SD)</th>
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<tr>
<td></td>
<td></td>
<td>59.5 (52.9–65.2)</td>
<td>922 (22.8%)</td>
<td>114 (2.8%)</td>
<td>3.0 (1.2–6.5)</td>
<td>1.25 (1.0)</td>
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<td>Comorbidity, n (%)</td>
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<tr>
<td>Heart failure</td>
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<td>320 (7.9%)</td>
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<tr>
<td>Hypertension</td>
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<td>1776 (43.8)%</td>
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<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>207 (5.1)</td>
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<td>Previous stroke</td>
<td></td>
<td>211 (5.2)</td>
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<tr>
<td>Vascular disease</td>
<td></td>
<td>276 (6.8)</td>
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<tr>
<td>Coronary heart disease</td>
<td></td>
<td>228 (5.6)</td>
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<tr>
<td>Periphery artery disease</td>
<td></td>
<td>63 (1.6)</td>
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<tr>
<td>Previous bleeding</td>
<td></td>
<td>178 (4.4)</td>
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<tr>
<td>Liver disease</td>
<td></td>
<td>46 (1.1)</td>
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<tr>
<td>Kidney disease</td>
<td></td>
<td>134 (3.3)</td>
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<td>Alcohol abuse</td>
<td></td>
<td>144 (3.6)</td>
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<td>CHA2DS2-VASc score, n (%)</td>
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<tr>
<td>0 (low risk)</td>
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<td>1275 (31.5)</td>
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<tr>
<td>1 (intermediate risk)</td>
<td></td>
<td>1268 (31.3)</td>
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<td>≥ 2 (high risk)</td>
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<td>1507 (37.2)</td>
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<td>HAS-BLED score, n (%)</td>
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<td>≤ 1 (low risk)</td>
<td></td>
<td>2530 (62.5)</td>
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<tr>
<td>2 (intermediate risk)</td>
<td></td>
<td>1015 (25.1)</td>
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<td>≥ 3 (high risk)</td>
<td></td>
<td>505 (12.5)</td>
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<td>Medication at baseline, n (%)</td>
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<tr>
<td>Warfarin</td>
<td></td>
<td>3707 (91.5)</td>
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<tr>
<td>Aspirin</td>
<td></td>
<td>1241 (30.6)</td>
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<td>Clopidogrel</td>
<td></td>
<td>37 (0.9)</td>
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<td>Triple therapy*</td>
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<td>21 (0.5)</td>
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<tr>
<td>Amiodarone</td>
<td></td>
<td>1026 (25.3)</td>
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<td>Class Ic – AADs</td>
<td></td>
<td>753 (18.6)</td>
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<tr>
<td>Sotalol</td>
<td></td>
<td>257 (6.1)</td>
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<tr>
<td>β-Blockers</td>
<td></td>
<td>2479 (61.2)</td>
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<tr>
<td>Digoxin</td>
<td></td>
<td>1055 (26.3)</td>
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<tr>
<td>Verapamil</td>
<td></td>
<td>576 (14.2)</td>
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<tr>
<td>Statin</td>
<td></td>
<td>1197 (29.5)</td>
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<tr>
<td>NSAIDs</td>
<td></td>
<td>521 (12.9)</td>
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</table>

IQR, interquartile range; AADs, antiarrhythmic drugs; NSAIDs, non-steroidal anti-inflammatory drugs.

*Triple therapy = simultaneous use of warfarin+aspirin+clopidogrel.

Persistence of Oral anticoagulation treatment after radiofrequency ablation
Oral anticoagulation was initiated in 3707 (91.5%) patients after RFA. Figure 1 depicts long-term persistence of OAC treatment according
to thromboembolic risk profile. At Day 90, 1181 (97.3%) of low-risk, 1140 (94.7%) of intermediate-risk, and 1450 (95%) of high-risk patients were on OAC therapy. Corresponding numbers at 1 year were lower; 55.7, 67.4, and 70.4%, respectively. Approximately 70% of high-risk patients and half of the total RFA population received OAC therapy beyond the first year.

**Thromboembolism and bleeding events**

After discharge from first-time RFA, 103 (2.5%) patients experienced thromboembolism (71 (68.9%) stroke, 27 (26.2%) TIA, and 5 (4.9%) peripheral arterial embolism) corresponding to an incidence rate of 0.80 [95% confidence interval (CI): 0.66–0.98] per 100 person-years. Of note, no patients in this cohort underwent left atrial appendage occlusion.

*Figure 2* shows the incidence rates of thromboembolism and serious bleeding according to time intervals after first-time RFA, illustrating high event rates for both outcomes immediately after RFA procedure. Among the 103 thromboembolism cases, 32 (31%) patients developed thromboembolism [incidence rate 3.27 (95% CI: 2.31–4.62) per 100 person-years] during the 3 months blanking period. After 3 months, 71 (69%) patients experienced thromboembolism [incidence rate 0.60 (95% CI: 0.48–0.76) per 100 person-years]; only 37 (52.1%) of thromboembolic events occurred in high-risk patients. In the 111 cases with serious bleeding, events during and after the blanking period occurred in 24 (21.6%) and 87 (78.4%) cases, respectively, corresponding to incidence rates of 2.45 (95% CI: 1.64–3.65) and 0.73 (95% CI: 0.60–0.90) per 100 person-years. The incidence rate of serious bleeding was 0.60 (95 CI: 0.46–0.80) per 100 person-years after the blanking period when patients with aspirin therapy were excluded.

**Effect of oral anticoagulation therapy**

*Table 2* shows the incidence rates of thromboembolism and serious bleeding after the 3 months blanking period according to OAC therapy with results from the uni- and multivariable analyses. Oral anticoagulation discontinuation was not associated with significantly increased thromboembolic risk in low- or high-risk patients. In intermediate-risk patients, thromboembolic risk was significantly increased in the multivariable adjusted analysis. Oral anticoagulation therapy was associated with higher incidence rates of serious bleeding compared with OAC discontinuation.

*Figure 3* depicts the 5-year cumulative incidence of thromboembolism and serious bleeding according to OAC therapy. Oral anticoagulation discontinuation was associated with 0.6% higher long-term risk of thromboembolism, while risk of serious bleeding was decreased by 1.8%.

**Matched analyses**

The present cohort was compared (1 : 4) with 15,848 non-ablated AF patients treated with rhythm-control therapy, i.e. 6180 (39%) on AADs, 6656 (42%) on DC, and 3012 (19%) receiving AADs+DC. Over 5-year follow-up, 1107 (7%) ‘no-RFA’ patients had thromboembolism with an overall incidence rate of 1.77 (1.67–1.88) 95% CI per 100 person-years, where thromboembolic rates per 100 person-years with and without OAC were 1.34 (1.21–1.49) 95% CI and 2.14 (1.98–2.30) 95% CI, respectively. Crude incidence rate ratio (RFA vs. no-RFA) favoured RFA and was 0.47 (0.39–0.57) 95% CI. Adjusted
incidence rate ratio controlling for use of OAC, Aspirin, Clopidogrel, and the components of the CHA2DS2-VASc score was 0.53 (0.43–0.65)95%CI and remained in favour of RFA.

**Patient-specific risk factors for thromboembolism and serious bleeding**

Figure 4 displays individual predictors of thromboembolism and serious bleeding. Recurrent AF was significantly associated with increased thromboembolic risk, and previous history of stroke/TIA was the only and strongest predictor associated with thromboembolism among the components of CHA2DS2-VASc score. Previous history of bleeding was the strongest predictor of serious bleeding, while OAC therapy, aspirin use, and kidney disease were also significantly associated with increased serious bleeding risk. These results were consistent in sensitivity analyses (Supplementary material online, Tables S3 and S4).
Discussion

We studied the long-term risk of thromboembolism and serious bleeding according to OAC therapy in a nationwide cohort of 4050 AF patients undergoing RFA in Denmark. This study has four main findings: (i) approximately half of the total population and 70% of high-risk patients remained on OAC beyond the first year after RFA; (ii) the thromboembolic risk was relatively low in patients undergoing RFA compared with a matched non-ablated AF cohort receiving rhythm-control therapy; (iii) thromboembolic risk reduction associated with OAC therapy after RFA was counterbalanced by serious bleeding risk; (iv) the CHA2DS2-VASc score was not optimal for discriminating high- or low-risk patients after RFA and only previous stroke was significantly associated with increased risk of thromboembolism among other components.

We observed the highest thromboembolic risk within the first 2 weeks after RFA, which has been previously revealed in an older single-centre study.20 Our study extends this that the initially high-thromboembolic rates decreased rapidly during the first 3 months after RFA, and remained stationary. Our findings are also in accordance with the 2012 HRS/EHRA/ECAS Expert consensus statement on catheter ablation of AF, where the incidence of thromboembolism associated with AF ablation is reported to be between 0 and 7%. We found considerably lower thromboembolic risk rates than reported previously in unselected AF populations, and the risk is under the threshold that has been considered appropriate for initiating OAC in guidelines.1,12,16 Conceivably, the relatively low thromboembolic rates after RFA could be attributable to more or less adequate anticoagulation because approximately half of the RFA cohort and ~70% of high-risk patients were apparently on OAC therapy throughout the follow-up, although the quality of OAC could not be investigated due to lack of INR values. Of note, a recent study investigated the stroke rates in age- and gender-matched populations, and found that RFA-treated AF patients had significantly lower stroke risk compared with AF patients without RFA.21 In line with these results, the thromboembolic risk after RFA was also lower in the present cohort compared with a matched non-ablated AF population on rhythm-control therapy after controlling for use of anticoagulant and antithrombotic medication as well as the components of CHA2-Ds2-VASc score.

The thromboembolic rates in patients with or without OAC therapy were comparable and the multivariable analysis showed no significant increase in the thromboembolic risk associated with OAC discontinuation, which was only associated with 0.6% higher cumulative risk of thromboembolism at 5 years. Of note, the number of thromboembolic events was very low, especially in high-risk patients who constituted 37% of the study population in whom OAC is indicated according to current guidelines. Expectedly, OAC therapy was significantly associated with increased risk of serious bleeding, although the event rates were low. Our results may indicate that serious bleeding risk associated with OAC therapy seems to outweigh the benefits for thromboembolic risk reduction after RFA. This interpretation, however, should be contemplated with caution due to low number of events.

Themistoclakis et al. evaluated the safety of OAC discontinuation after RFA in a multicentre non-randomized study, including 3355 patients over 28 ± 23 months of follow-up.22 Similar to our results, the authors reported that although the stroke rates did not differ significantly by OAC therapy, the risk of major bleeding was significantly higher in patients receiving OAC therapy. Low stroke rates in off-OAC group favoured the safety of OAC discontinuation beyond post-operative 3 months. However, off-OAC group comprised only a few high-risk patients and the thromboembolic events within 3–6 months after RFA in patients discontinuing OAC were disregarded, providing a possible explanation to higher event rates in our study as the risk was highest during this period. Other studies have found similar results.20,23–25

Recurrence of AF was significantly associated with increased thromboembolic risk (Figure 4), as previously suggested.26 In a single-centre study, Nademanee et al. investigated 635 high-risk AF patients after

![Figure 3](image-url) The cumulative incidences of thromboembolism and serious bleeding according to oral anticoagulation therapy. (A) Thromboembolism, adjusted for the components of CHA2DS2-VASc score and (B) serious bleeding, adjusted for the components of HAS-BLED score.
AF ablation, and found that for patients in sinus rhythm discontinuing OAC the estimated 5-year stroke incidence was 3% compared with 23% in patients who remained on AF and continued warfarin. The authors concluded that successful AF ablation might allow for OAC discontinuation. Similar to that of the study by Themistoclakis, the follow-up was short and patients with recurrent AF reinstated warfarin therapy, which may have underestimated stroke rates in off-OAC group in both studies. In accordance with previous and our findings, a recent single-centre study by Winkle et al. also reported that OAC discontinuation may be safe in high-risk patients with prior stroke/TIA after successful RFA who may be able to discontinue OAC due to low-thromboembolic risk. Of note, these patients underwent regular standardized ECG follow-up screening for AF recurrences, whereas AF recurrences were determined from reviewing hospital records in 211 patients in our study without standardized Holter or ECG monitoring, which limits the interpretation of data as this might be a major influencing factor for thromboembolic events.

The CHADS2, CHA2DS2-VASc scores as well as renal disease have been associated with increased thromboembolic risk and suggested as independent predictors of late stroke after RFA. Renal disease did not qualify for inclusion in our

![Figure 4](image-url) Individual predictors associated with thromboembolism and serious bleeding after first-time radiofrequency ablation. (A) Thromboembolism, HR (95% CIs) and (B) serious bleeding, HR (95% CIs).
multivariable analysis, and we found that the individual components of CHA2DS2-VASc score represented different levels of thromboembolic risk after RFA, which seem to be driven primarily by previous stroke. Of note, the thromboembolic rates were similar between CHADS2, R2 CHADDS2, and CHA2DS2-VASc for scores ≥3, and the number of events was very low to make an adequate comparison for scores ≥4 (Supplementary material online, Table S5). Almost 70% of the cohort were classified as having intermediate- or high-thromboembolic risk according to the CHA2DS2-VASc score and therefore qualified for long-term OAC therapy according to guidelines. However, the clinical benefit of OAC therapy in this selected group of patients after RFA was negligible. This suggests that the CHA2DS2-VASc score may not be suitable for thromboembolic risk stratification to initiate or maintain OAC therapy in AF patients undergoing RFA.

The persistence of OAC therapy demonstrated a high long-term use of OAC in low-risk patients although the indication for treatment was lacking according to guidelines. This indicates a discrepancy between recommendations and real-life practice in use of OAC therapy after RFA. It is also interesting to investigate whether the novel anticoagulants have better safety and effectiveness profile compared with warfarin after RFA. This was difficult to evaluate in this cohort as Dabigatran became available very late in the study period in Denmark (August 2011), and only 80 (2%) patients claimed Dabigatran prescriptions after RFA, providing a very short total exposure duration (i.e. 13 person-years that was excluded from the analyses), during which no thromboembolic or bleeding events occurred.

Implications

Our study highlights relatively low long-term risk of thromboembolism after RFA independent of CHA2DS2-VASc score. Oral anticoagulation discontinuation seems to have no clinically significant effect on thromboembolic risk reduction but the number of thromboembolic events was very low to make definite conclusions especially in high-risk patients. Although bleeding risk associated with OAC therapy was also low, serious bleeding risk associated with OAC therapy might outweigh the benefit of OAC on thromboembolic risk reduction. This critical hypothesis should be tested in randomized studies enrolling large number of preferably high-risk patients to test our findings.

Limitations and strengths

The major limitation of the present study is inherited in its observational nature. No information was available on clinical the decision to discontinue or maintain OAC therapy. Further, we did not have information on INR values and the quality of OAC therapy. Recurrent AF might be underestimated since the registries do not include clinical data as recurrent AF was defined from AF-related hospitalizations and re-ablation procedures. Similarly, the absence of blood pressure measurements and blood glucose levels might have resulted in exclusion of undiagnosed hypertension and diabetes mellitus.

Although the epidemiological approach entails such limitations, our study reflects real-life clinical practice on a nationwide scale in a large unselected population with long-term follow-up. Moreover, the methods and the outcome measures were previously validated and found accurate. Additionally, the nationwide registries include all patients irrespective of participation in the labour market, and are not affected by selection bias caused by including selected age groups, hospitals, and health insurance systems.

Conclusion

In an unselected AF population undergoing RFA thromboembolic risk beyond 3 months after RFA was relatively low compared with a matched non-ablated AF cohort. The CHA2DS2-VASc score may not be an appropriate tool for thromboembolic risk stratification. With cautious interpretation due to low number of events, risk of serious bleeding associated with OAC might outweigh the benefits of thromboembolic risk reduction after RFA. Randomized studies are warranted to test our results.

Supplementary material

Supplementary material is available at European Heart Journal online.

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References


