Renal Dysfunction, Stroke Risk Scores (CHADS2, CHA2DS2-VASc and R2CHADS2) and the Risk of Thromboembolic Events after Catheter Ablation of Atrial Fibrillation: The Leipzig Heart Center AF Ablation Registry

Running title: Kornej et al.; Stroke predictors after AF ablation

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Abstract:

**Background** - There are limited data on the predictive value of stroke risk scores for thromboembolic events (TE) after catheter ablation of atrial fibrillation (AF). Our objectives were to report the incidence of TE after AF ablation in a large contemporary AF ablation cohort.

**Methods and Results** - Using the Leipzig Heart Center AF Ablation Registry, we documented TE in patients undergoing radiofrequency AF catheter ablation. TE was defined as stroke, transient ischaemic attack (TIA) or systemic embolism.

Study population (n=2,069, 66% male, 60±10 years; 62% paroxysmal AF; mean CHADS2 1.2 ± 0.9, CHA2DS2-VASc 2.1 ± 1.4 and R2CHADS2 1.3 ± 1.1) were followed-up for a median 18 [Q1-to-Q3 12–29] months (i.e. 3.078 patient-years). Overall 31 TE occurred, with 16 events within 30 days of ablation and 15 TE (0.72%) during the follow-up period. On multivariate analysis, CHADS2 (p<0.001), R2CHADS2 (p<0.001), CHA2DS2-VASc (p=0.003) scores were independent predictors of TE during follow-up and AF recurrence conferred a non-significant trend for increased TE risk (p=0.071 – 0.094). The CHA2DS2-VASc score further differentiated TE risk in patients with CHADS2 and R2CHADS2 0–1 (0.13% if CHA2DS2-VASc was 0–1 and 0.71% if CHA2DS2-VASc was >2) and had the best predictive value in patients with AF recurrences (c-index 0.894, p=0.022 vs CHADS2, p=0.031 vs R2CHADS2).

**Conclusions** - CHADS2, CHA2DS2-VASc, R2CHADS2 scores were associated with TE risk. The CHA2DS2-VASc score differentiated TE risk in the “low” risk strata based on CHADS2 and R2CHADS2 scores, and may be superior in the subgroup with AF recurrences.

**Key words:** atrial fibrillation, catheter ablation, thromboembolic complication, AF recurrence, CHA2DS2-VASc score
Introduction

Catheter ablation of atrial fibrillation (AF) is an effective therapy for the reduction of AF burden, improvement of symptoms and quality of life. Major complications occur between 3.9% and 5.1% and can include thromboembolic complications in 1%. While the thromboembolic risk seems to be increased post-ablation there is the suggestion of a reduction in thromboembolic event (TE) rates during long-term follow-up. Observational and registry studies have demonstrated low annual rates of TE (strokes and systemic embolism) during medium-term follow-up after AF catheter ablation ranging between 0.5% and 1.7%, thus reaching event rates that are broadly comparable to patients without AF.

There are only limited data on risk prediction scores for TE after AF ablation. Although previous studies suggest that both the CHADS2 and CHA2DS2-VASc score, as well as renal dysfunction are useful predictors for thromboembolic complications after ablation, they are hampered by small sample sizes, inclusion of few high-risk patients, incomplete follow-up, and an unknown number of patients on anticoagulation with possible underuse.

Renal dysfunction was incorporated in the R2CHADS2 risk score by adding 2 additional points for eGFR<60 ml/min/1.73 m² as an additional risk factor to the CHADS2 score, and demonstrated marginal additive predictive power over the CHADS2 score in predicting TE in a selected anticoagulated trial patient cohort with non-valvular AF while in ‘real world’ cohorts, renal impairment did not independently add to stroke risk scores to improve their predictive value. Despite this controversy this score has not been evaluated in AF patients after catheter ablation.

Our objectives were to report the incidence of TE (and its predisposing factors) after AF ablation in a large contemporary AF ablation registry and second, to investigate the impact of
renal dysfunction and the value of stroke risk stratification scores (CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc and R<sub>2</sub>CHADS<sub>2</sub>) for predicting TE after AF ablation.

**Methods**

**Patients and risk scores**

The study population comprised 2,069 consecutive patients with symptomatic AF who underwent radiofrequency (RF) catheter ablation at the Heart Center Leipzig between January 2007 and December 2011. Stroke risk was assessed using the CHADS<sub>2</sub> (Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, and history of Stroke/transient ischemic attack (2 points))<sup>15</sup> and CHA<sub>2</sub>DS<sub>2</sub>-VASc (Congestive heart failure, Hypertension, Age > 75 years (2 points), Diabetes mellitus, and history of Stroke/transient ischemic attack (2 points) – Vascular disease (history of myocardial infarction, peripheral artery disease or vascular plaques), Age 65 – 74 years, and Sex category [female]) scores<sup>16, 17</sup>. The R<sub>2</sub>CHADS<sub>2</sub> score incorporated the components of the CHADS<sub>2</sub> score and also gave 2 points for renal dysfunction defined as estimated glomerular filtration rate (eGFR)<60 mL/min.<sup>12</sup> eGFR was calculated by using the Cockroft-Gault equation: (140 – age) x weight (kg) x (0.85 if female) / 72 x serum creatinine (mg/dl).

**Catheter ablation and follow-up**

Left atrial catheter ablation was performed using a previously described approach.<sup>18</sup> Patients presenting with AF at the beginning of the procedure were electrically cardioverted and ablation was performed during sinus rhythm (i.e. AF termination with ablation was not attempted). In all patients circumferential left atrial ablation lines were placed around the antrum of the ipsilateral pulmonary veins (irrigated tip catheter, pre-selected tip temperature of 48°C, and maximum
power of 30–50 W). In patients with persistent AF, additional linear lesions were added at the left atrial roof, the basal posterior wall and the left atrial isthmus and according to low voltage areas. Ablation of complex fractionated electrograms was not performed. After circumferential line placement, voltage and pace mapping along the ablation line were used to identify and close gaps. The isolation of all pulmonary veins with bidirectional block was verified with a multipolar circular mapping catheter and was defined as the procedural endpoint. After ablation, class I and III antiarrhythmic drugs were not reinitiated, and proton pump inhibitors were added for 4 weeks.

According to the current guidelines, oral anticoagulation was prescribed for 3-6 months after ablation and depending on the CHADS2 or CHA2DS2-VASc scores thereafter. Because of patient preferences, lack of symptoms and ECG recordings of sinus rhythm it was replaced by aspirin in some patients.

All patients were followed in the outpatient clinic for at least 12 months after the catheter ablation. During follow-up, serial 7-day Holter ECG recordings were performed immediately, and at 3, 6 and 12 months after the procedure. Additional ECGs and Holter ECG recordings were obtained when patients’ symptoms were suggestive of AF. AF recurrence was defined as a documented atrial arrhythmia episode lasting longer than 30 seconds after a 3 months “blanking period”.

Outcomes

The primary endpoint of this study was the composite of ischaemic stroke, transient ischaemic attack (TIA) and/or systemic embolism during follow-up excluding events within the first 30 days after ablation. Ischaemic stroke was a clinical diagnosis that was made on the basis of typical symptoms lasting at least 24 hours. Brain imaging, which was available in the vast
majority of patients, was not required but was recommended for the general diagnosis of stroke. A TIA was defined as sudden-onset focal neurological deficit with duration of < 24 hours. Systemic embolism was defined as TE events that occurred in peripheral organs (e.g. spleen) or extremities.

Statistical analysis
Data are presented as means and standard deviation for normally distributed continuous variables and as proportions for categorical variables. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. The differences between continuous values were assessed using an unpaired two-tailed t-test for normally distributed continuous variables, a Mann – Whitney test for skewed variables, and a chi-square test for nominal variables.

Cox regression analyses was used to identify factors associated with thromboembolic events (stroke, TIA, systemic embolism). Multivariable analysis, which included variables with a p-value <0.1 found on univariate analysis, was performed to identify independent predictors of TE. In addition, we performed multivariate analysis separately for every stroke risk stratification score with adjustment for renal dysfunction (for the CHADS2 and CHA2DS2-VASc scores) or peripheral artery disease (for the CHADS2 and R2CHADS2 scores).

ROC (receiver operating characteristic) curves were generated for graphical illustration of CHADS2, R2CHADS2 and CHA2DS2-VASc scores’ performance in predicting TE, with the area under the curve (AUC) being equivalent to the c-index for determining the predictive value for a score. The c-indexes (ie. areas under the ROC curves) for the 3 scores were compared by using DeLong’s method.20 A p value of < 0.05 was considered statistically significant. All analyses were performed with SPSS statistical software version 17.
Results

Patient characteristics and thromboembolic events

The clinical characteristics are summarized in Table 1. Complete rhythm follow-up was available in 1,557 patients (75.3%) revealing AF recurrences in 25.8%.

Overall, TE occurred in 31 patients (1.5%). Sixteen patients (0.8%) suffered TE within first 30 days after catheter ablation.

During the follow-up period of median [Q1-to-Q3] 18 [12 – 29] months (3,078 patient-years), 15 (0.72%) experienced TE, including 5 ischemic strokes, 9 TIAs, and 1 systemic embolism. The characteristics of those patients with TE events during follow-up are shown in a supplementary Table (Table e1). The median [Q1-to-Q3] time to event was 11 [6 - 19] months. All patients with TE were anticoagulated at the time of event. The mean INR at discharge for the patients on VKA in TE cohort was 1.5 ± 0.5 and 2.37 ± 0.75 at the time of TE.

Common risk scores as predictors of thromboembolic events

Patients with TE had more frequently a history of previous TE, renal dysfunction and recurring AF as well as higher CHADS2, R2CHADS2 and CHA2DS2-VASc scores (Table 1). Using 3 separate multivariate Cox regression (Table 2) analyses of the entire cohort, the CHADS2, R2CHADS2 and CHA2DS2-VASc scores were significant predictors of TE events.

Based on ROC curve analysis, all three risk stratification scores had good predictive value (c-indexes 0.720 [0.700-0.739] for CHADS2 and 0.736 [0.716-0.755] for both R2CHADS2 and CHA2DS2-VASc scores) for predicting TE (p<0.05 for all scores) without any significant difference among the scores (Figure 1). As shown in Figure 2, the CHA2DS2-VASc score was able to further differentiate TE risk in patients with CHADS2 and R2CHADS2 0–1. In those
patients, TE occurred in 0.13% if CHA2DS2-VASc was 0–1 and 0.62–0.71% if the CHA2DS2-VASc score was ≥2.

There was no association between antiarrhythmic drug usage after catheter ablation and TE at follow up (p=0.810). Anticoagulation regimes at discharge and at 6 month follow up were also not associated with TE (p=0.901 and p=0.138).

Impact of AF recurrences

The importance of AF recurrences on TE occurrence after catheter ablation was examined in a subgroup of 1,557 patients (75.3 %) with complete rhythm follow up data

Predictors for TE in patients with available rhythm outcomes are presented in Table e2. All three stroke risk stratification scores were associated with TE, while AF recurrence conferred a non-significant trend for increased TE risk (depending on the multivariable model p=0.056 – 0.077).

In patients with AF recurrence (n=402, 26%), all three risk scores were also associated with TE (Table e3) with the CHA2DS2-VASc score having the best c-index (0.894, 95% CI 0.860-0.923) (Figure e1), superior to CHADS2 (p=0.022) and R2CHADS2 (p=0.031).

Discussion

To the best of our knowledge, this is the largest study assessing the incidence and risk factors for thromboembolic complications after AF catheter ablation during mid-term follow-up with a special focus on renal dysfunction and stroke risk stratification scores. The main findings are that TE after AF catheter ablation are rare, but all three stroke risk stratification scores, i.e. CHADS2, CHA2DS2-VASc, R2CHADS2 are associated with TE risk. The CHA2DS2-VASc was useful to differentiate stroke risk in “low” thromboembolic risk strata according to the CHADS2 and
R₂CHADS₂ scores. Also, the CHA₂DS₂-VASc had the best predictive value for TE in the subgroup with AF recurrences.

Several studies have suggested lowered stroke rates following catheter ablation.²¹,²² With 4,212 patients included and followed for at least 3 years, Bunch et al⁹ reported that AF ablation may not only reduce stroke, but also reduced mortality risk compared to AF patients without ablation, with event rates even reaching levels seen amongst patients without AF. More recently, Lin et al¹¹ reported a small cohort showing a significant risk reduction of TE in patients after catheter ablation compared to those who received antiarrhythmic medication (2.3 % versus 8.6 %). In our study with >2000 patients with drug-refractory AF undergoing catheter ablation, we have observed a low rate of TE which is in accordance with several studies.⁷,⁸ The strength of our study is the use of a large contemporary cohort of consecutive patients undergoing ablation therapy for AF with guideline-adherent peri- and post-procedural anticoagulation.

The importance of CHADS₂ and CHA₂DS₂-VASc scores in prediction of long-term cardiovascular outcomes and mortality has been of interest for several years.¹¹,²³,²⁴ There are only limited data on stroke predictors in patients after AF catheter ablation. Chao et al⁴ demonstrated that both CHADS₂ and CHA₂DS₂-VASc scores could provide an estimation of the risk of adverse events in patients undergoing catheter ablation. More recently, the same group demonstrated the predictive value of added renal dysfunction to the CHA₂DS₂-VASc score, as an additional risk factor for TE, with a small but significant improvement in prediction value for thromboembolism.¹⁰ However, there were limited patient numbers with relatively high occurrence of TE (2.9 %) perhaps due to a high percentage of non-anticoagulated patients.

We did not find a significant independent effect of renal dysfunction on TE risk, and this may reflect that many of the risk factor components of CHADS₂ and CHA₂DS₂-VASc scores
(that is, age, heart failure, diabetes, vascular disease etc) are themselves related to renal
dysfunction. The association between renal dysfunction and thromboembolism in the general
population as well as its role in AF-related strokes is well known and has been studied for
several years.\textsuperscript{25-27} In the ATRIA study, proteinuria and reduced estimated glomerular filtration
rate were associated with a significant TE risk increase.\textsuperscript{28} In the Danish National Patient
Registry, renal failure increased stroke risk up to 83\%.\textsuperscript{25} In another study, eGFR<60
mL/min/1.73 m\textsuperscript{2} was a significant predictor of stroke and cardiovascular events among patients
with AF, independent of the CHADS\textsubscript{2} score,\textsuperscript{29} in accordance with recently published studies.\textsuperscript{25,30}

Despite the known association between renal dysfunction and TE in AF, ‘renal
dysfunction’ has not been included in any of the current stroke stratification schemes, although it
was previously proposed that the small ‘c’ in CHA\textsubscript{2}DS\textsubscript{2}-VASc score could informally represent
chronic renal impairment.\textsuperscript{31} In 2012, Piccini et al\textsuperscript{12} proposed the R\textsubscript{2}CHADS\textsubscript{2} score, in which
renal dysfunction (eGFR< 60mL/min/1.73 m\textsuperscript{2} using Cockroft-Gault formula) was assigned 2
points – but this was derived from anticoagulated clinical trial cohort, where the whole range of
renal function was not studied (patients with eGFR<30ml/min were excluded) and the broad
range of stroke risk was not evident (the trial population excluded those with a CHADS\textsubscript{2} scores
0-1 and even CHADS\textsubscript{2}=2 was capped at 10\%). In the ‘real-life’ cohorts studying a broad range
of stroke risk, renal function and non-anticoagulated subjects, an independent additive value of
renal dysfunction to risk scores for TE was not found.\textsuperscript{30,32} In accordance with some previous
studies, we found that CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc scores had strong predictive value for TE
during medium-term follow up in non-valvular AF.\textsuperscript{4,11} A new observation in our study was the
use of R\textsubscript{2}CHADS\textsubscript{2} in the prediction of TE but there was no added advantage of this score
compared to the ‘classic’ CHADS2 and CHA2DS2-VASc scores.

In the nationwide Danish cohort study, Olesen et al. found that those defined as ‘low’ risk using a CHADS2 score=0 had a stroke risk ranging from 0.8% to 3.2%/year, suggesting improved of classification of AF patients without OAC at low and moderate risk for TE, when compared to CHADS2 score. Similar results had been shown in a trial cohort of patients with CHADS2 score =1 and treated with antiplatelet therapy, where a very low risk group (1% per year stroke risk) was separated from other patients. Potpara et al. found that CHA2DS2-VASc offered best predictive performance for the absence of ischaemic stroke when compared to the CHADS2 and van Walraven scores.

In our study, we show the usefulness of CHA2DS2-VASc score to further discrimination those patients classed as being at ‘low-moderate’ risk by the CHADS2 and R2CHADS2 scores of 0 or 1. Although patients with ‘low’ CHADS2 and R2CHADS2 seemed to have a lower risk for TE compared to those with a score ≥2, further subanalysis of these groups using the CHA2DS2-VASc score re-classified patients into a truly low or moderate risk (CHA2DS2-VASc = 0-1) and high risk (CHA2DS2-VASc ≥2). Our data show almost the same TE risk (0.71% and 0.62%) with a previous study although their event rate was much higher. In the subgroup followed up for AF recurrence, the CHA2DS2-VASc score has the best c-index compared to CHADS2 or R2CHADS2.

Hunter et al. demonstrated that an AF ablation strategy was associated with lower rates of stroke and death over the long term compared with patients on medical treatment. It remains possible that AF is a risk marker of more serious cardiac disease rather than a causative factor, and freedom from AF was the strongest predictor of stroke-free survival. Although the association between TE and AF recurrences in our subpopulation did not reach significance, our results demonstrated a 4.2-fold risk for TE in patients with AF relapses in univariate analyses.
Similar to previous data, we did not find any association between antiarrhythmic drug use after catheter ablation and TE events at follow up. Of note, anticoagulation regimes at discharge and at 6 month follow up were also not associated with TE events but the majority of our patients were anticoagulated.

Limitations

This study is limited by its registry design, although we had careful follow up data in a large consecutive series. Prospective randomized trials are required to confirm whether the incidence of TE is reduced in the catheter ablation-treated patients. We had relatively low event rates, but on ROC curve analysis all scores exhibited broadly similar prediction levels. The ability of the CHA2DS2-VASc score to discriminate between high and low risk patients using net reclassification improvement (NRI) was also restricted by the low number of events.

Taken together, although the low event rate may affect statistical power, our findings are consistent and reveal plausible associations.

Rhythm follow-up was complete in 75% but underdetection of silent AF remains an issue that may contribute to the non-significance of AF recurrences as TE predictor. Finally, TE was assumed to be thromboembolic based on clinical history and brain imaging but other etiologies may be possible.

In conclusion, TE after AF catheter ablation are rare, but all three stroke risk stratification scores, i.e. CHADS2, CHA2DS2-VASc, R2CHADS2 were associated with TE risk. The CHA2DS2-VASc score was useful to differentiate TE risk in the “low” thromboembolic risk strata based on CHADS2 and R2CHADS2 scores, and may be superior in the subgroup with AF recurrences. It is important to stress that the risk scores were useful in light of AF reduction by catheter ablation and use of anticoagulation. This suggests that high-risk patients identified by
the risk scores would need optimized anticoagulation through intensified warfarin therapy or novel oral anticoagulants and/or intensified rhythm control. However, further studies are needed to address and support this concept.

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**Conflict of Interest Disclosure:** None.

**References:**


score of 1 who are unlikely to benefit from oral anticoagulant therapy. [In press]. Eur Heart J. 2013;34:170-176.


Table 1. Baseline characteristics of the study population and stratified according to TE events during follow-up

<table>
<thead>
<tr>
<th></th>
<th>Total (n=2,069)</th>
<th>TE in FU [n=2,054]</th>
<th>p-value</th>
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<tr>
<td>Age, years</td>
<td>60 ± 10</td>
<td>60 ± 10</td>
<td>64 ± 11</td>
</tr>
<tr>
<td>Males</td>
<td>66</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>AF type (paroxysmal)</td>
<td>63</td>
<td>63</td>
<td>53</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28 ± 5</td>
<td>29 ± 5</td>
<td>27 ± 5</td>
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<td>eGFR, ml/min/1.73 m²</td>
<td>100 ± 34</td>
<td>100 ± 34</td>
<td>88 ± 25</td>
</tr>
<tr>
<td>Hypertension</td>
<td>71</td>
<td>71</td>
<td>93</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<td>15</td>
<td>27</td>
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<tr>
<td>Coronary artery disease</td>
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<td>14</td>
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<td>Chronic heart failure</td>
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<td>7</td>
<td>13</td>
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<tr>
<td>Peripheral artery disease</td>
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<td>8</td>
<td>20</td>
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<tr>
<td>Renal dysfunction</td>
<td>7</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Previous thromboembolic events</td>
<td>9</td>
<td>9</td>
<td>33</td>
</tr>
<tr>
<td>Peri-interventional stroke/TIA</td>
<td>0.8</td>
<td>0.8</td>
<td>0</td>
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<tr>
<td>CHADS2</td>
<td>1.2 ± 0.9</td>
<td>1.2 ± 0.9</td>
<td>2.1 ± 1.3</td>
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<td>R²CHADS2</td>
<td>1.3 ± 1.1</td>
<td>1.3 ± 1.1</td>
<td>2.5 ± 1.6</td>
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<tr>
<td>CHA²DS²-VASc</td>
<td>2.1 ± 1.4</td>
<td>2.1 ± 1.4</td>
<td>3.5 ± 1.7</td>
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<tr>
<td>LV-EF, %</td>
<td>59 ± 10</td>
<td>59 ± 10</td>
<td>53 ± 16</td>
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<tr>
<td>LV-EDd, mm</td>
<td>49 ± 8</td>
<td>49 ± 7</td>
<td>51 ± 12</td>
</tr>
<tr>
<td>LAD, mm</td>
<td>43 ± 6</td>
<td>43 ± 6</td>
<td>45 ± 9</td>
</tr>
<tr>
<td>Number of ablations</td>
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<tr>
<td>mean ± SD</td>
<td>1.42 ± 0.73</td>
<td>1.42 ± 0.73</td>
<td>1.47 ± 0.74</td>
</tr>
<tr>
<td>AF recurrence*</td>
<td>25.8</td>
<td>25.6</td>
<td>53.3</td>
</tr>
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</table>

FU – follow up, BMI – body mass index, eGFR – estimated glomerular filtration rate, LV-EF - left ventricular ejection fraction, LV-EDd – left ventricular end-diastolic diameter, LAD - left atrial diameter

* complete rhythm follow-up was available for 1,557 patients
Table 2. Clinical predictors for TE events in the entire cohort (n=2,069)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cox regression</th>
<th>UV</th>
<th>MV*</th>
<th>Model 1</th>
<th>MV</th>
<th>Model 2</th>
<th>MV</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR 95% CI</td>
<td>P-value</td>
<td>HR 95% CI</td>
<td>P-value</td>
<td>HR 95% CI</td>
<td>P-value</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>5.3   0.69 – 40.4</td>
<td>0.107</td>
<td>2.2  0.61 – 8.0</td>
<td>0.229</td>
<td>2.2  0.6 – 7.8</td>
<td>0.241</td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td></td>
<td>3.2   0.89 – 11.3</td>
<td>0.093</td>
<td>2.2  0.61 – 8.0</td>
<td>0.229</td>
<td>2.2  0.6 – 7.8</td>
<td>0.241</td>
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</tr>
<tr>
<td>Previous TE</td>
<td></td>
<td>5.3   1.8 – 15.4</td>
<td><strong>0.002</strong></td>
<td>2.2  0.61 – 8.0</td>
<td>0.229</td>
<td>2.2  0.6 – 7.8</td>
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<tr>
<td>RD</td>
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<td>3.5   0.99 – 12.5</td>
<td>0.052</td>
<td>2.2  0.61 – 8.0</td>
<td>0.229</td>
<td>2.2  0.6 – 7.8</td>
<td>0.241</td>
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<tr>
<td>CHADS2</td>
<td></td>
<td>2.0   1.4 – 2.9</td>
<td>&lt;<strong>0.001</strong></td>
<td>1.9   1.3 – 2.8</td>
<td><strong>0.001</strong></td>
<td>1.9   0.52 – 7.1</td>
<td>0.327</td>
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<tr>
<td>R2CHADS2</td>
<td></td>
<td>1.8   1.4 – 2.5</td>
<td>&lt;<strong>0.001</strong></td>
<td>1.8   1.3 – 2.4</td>
<td><strong>&lt;0.001</strong></td>
<td>1.9   0.52 – 7.1</td>
<td>0.327</td>
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<tr>
<td>CHA2DS2-VASe</td>
<td></td>
<td>1.7   1.3 – 2.3</td>
<td>&lt;<strong>0.001</strong></td>
<td>1.6   1.2 – 2.2</td>
<td><strong>0.001</strong></td>
<td>1.6   1.2 – 2.2</td>
<td><strong>0.001</strong></td>
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</tbody>
</table>

Abbreviations: UV – univariate analysis, MV – multivariate analysis, PAD – peripheral artery disease, TE – thromboembolic events, RD – renal dysfunction (eGFR <60 ml/min/1.72m²)
* Although hypertension and previous TE had a p value <0.1 in univariate analysis, we did not include them into multivariate analysis due to their inclusion in to all risk scores.
Figure Legends:

Figure 1. ROC curves for the CHADS2, CHA2DS2-VASc and R2CHADS2 scores in predicting TE events in the entire cohort (n=2,069). Significance levels: CHADS2 vs R2CHADS2 - p=0.617, CHADS2 vs CHA2DS2-VASc - p=0.674, R2CHADS2 vs CHA2DS2-VASc - p=0.996

Abbreviations: AUC– area under the curve (equivalent to c-index)

Figure 2. TE events according to different scoring systems. A. CHADS2 score. B. R2CHADS2 score.
Renal Dysfunction, Stroke Risk Scores (CHADS2, CHA2DS2-VASc and R2CHADS2) and the Risk of Thromboembolic Events after Catheter Ablation of Atrial Fibrillation: The Leipzig Heart Center AF Ablation Registry

Jelena Kornej, Gerhard Hindricks, Jedrzej Kosiuk, Arash Arya, Philipp Sommer, Daniela Husser, Sascha Rolf, Sergio Richter, Christopher Piorkowski, Thomas Gaspar, Gregory Y.H. Lip and Andreas Bollmann

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### eTable 1. Clinical characteristics of patients with TE events

<table>
<thead>
<tr>
<th></th>
<th>Gender</th>
<th>Age</th>
<th>CHADS₂</th>
<th>R₂CHADS₂</th>
<th>CHA₂DS₂-VASc</th>
<th>eGFR ml/min/1.73m²</th>
<th>Event</th>
<th>Time to event (months)</th>
<th>OAC</th>
<th>AF recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Female</td>
<td>32</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>80</td>
<td>Stroke</td>
<td>2</td>
<td>Aspirin, clopidogrel, LMWH*</td>
<td>no</td>
</tr>
<tr>
<td>#2</td>
<td>Male</td>
<td>54</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>&gt;100</td>
<td>Stroke</td>
<td>37</td>
<td>Warfarin</td>
<td>no</td>
</tr>
<tr>
<td>#3</td>
<td>Female</td>
<td>54</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>69</td>
<td>Stroke</td>
<td>11</td>
<td>LMWH</td>
<td>yes</td>
</tr>
<tr>
<td>#4</td>
<td>Female</td>
<td>57</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>&gt;100</td>
<td>Stroke</td>
<td>24</td>
<td>Warfarin</td>
<td>no</td>
</tr>
<tr>
<td>#5</td>
<td>Male</td>
<td>58</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>100</td>
<td>Stroke</td>
<td>16</td>
<td>Warfarin</td>
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<tr>
<td>#6</td>
<td>Male</td>
<td>64</td>
<td>3</td>
<td>3</td>
<td>4</td>
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<td>Stroke</td>
<td>5</td>
<td>Aspirin, clopidogrel</td>
<td>no</td>
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<tr>
<td>#7</td>
<td>Male</td>
<td>64</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>75</td>
<td>TIA</td>
<td>9</td>
<td>Dabigatran</td>
<td>no</td>
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<tr>
<td>#8</td>
<td>Male</td>
<td>66</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>59</td>
<td>A. poplitea embolism</td>
<td>40</td>
<td>Warfarin</td>
<td>yes</td>
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<tr>
<td>#9</td>
<td>Female</td>
<td>68</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>88</td>
<td>TIA</td>
<td>6</td>
<td>Warfarin</td>
<td>yes</td>
</tr>
<tr>
<td>#10</td>
<td>Female</td>
<td>69</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>77</td>
<td>TIA</td>
<td>15</td>
<td>Warfarin</td>
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<tr>
<td>#11</td>
<td>Male</td>
<td>71</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>93</td>
<td>TIA</td>
<td>5</td>
<td>Warfarin</td>
<td>yes</td>
</tr>
<tr>
<td>#12</td>
<td>Male</td>
<td>72</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>97</td>
<td>TIA</td>
<td>11</td>
<td>Warfarin</td>
<td>yes</td>
</tr>
<tr>
<td>#13</td>
<td>Male</td>
<td>72</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>58</td>
<td>TIA</td>
<td>3</td>
<td>Warfarin</td>
<td>no</td>
</tr>
<tr>
<td>#14</td>
<td>Male</td>
<td>76</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>55</td>
<td>Stroke</td>
<td>10</td>
<td>Warfarin</td>
<td>yes</td>
</tr>
<tr>
<td>#15</td>
<td>Female</td>
<td>76</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>82</td>
<td>TIA</td>
<td>17</td>
<td>Warfarin</td>
<td>yes</td>
</tr>
</tbody>
</table>

* status post pulmonary venous stent due to pulmonary vein stenosis
Abbreviation: LMWH – low molecular weight heparin
**eTable 2.** Clinical predictors for TE events in cohort with complete follow up for rhythm outcomes (n=1,557)

<table>
<thead>
<tr>
<th>Variables</th>
<th>UV</th>
<th>MV Model 1</th>
<th>MV Model 2</th>
<th>MV Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI P-value</td>
<td>HR 95% CI P-value</td>
<td>HR 95% CI P-value</td>
<td>HR 95% CI P-value</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.6 0.73–42.5 0.097</td>
<td>2.2 0.59–8.0 0.329</td>
<td>2.2 0.6–8.2 0.230</td>
<td>_ _ _ _ _ _ _</td>
</tr>
<tr>
<td>PAD</td>
<td>3.7 1.02–13.0 <strong>0.046</strong></td>
<td>2.2 0.62–8.2 0.220</td>
<td>_ _ _ _ _ _ _</td>
<td>_ _ _ _ _ _ _</td>
</tr>
<tr>
<td>Previous TE</td>
<td>5.8 2.0–17.1 <strong>0.001</strong></td>
<td>_ _ _ _ _ _ _</td>
<td>_ _ _ _ _ _ _</td>
<td>_ _ _ _ _ _ _</td>
</tr>
<tr>
<td>RD</td>
<td>3.9 1.1–14.0 <strong>0.034</strong></td>
<td>2.2 0.62–8.2 0.220</td>
<td>1.8 0.48–6.7 0.386</td>
<td>_ _ _ _ _ _ _</td>
</tr>
<tr>
<td>AF recurrences</td>
<td>3.4 1.2–9.3 <strong>0.019</strong></td>
<td>2.6 0.92–7.4 0.071</td>
<td>2.6 0.9–7.2 0.077</td>
<td>2.7 0.98–7.7 0.056</td>
</tr>
<tr>
<td>CHADS2</td>
<td>2.1 1.5–3.0 &lt;0.001</td>
<td>1.9 1.3–2.8 <strong>0.001</strong></td>
<td>_ _ _ _ _ _ _</td>
<td>_ _ _ _ _ _ _</td>
</tr>
<tr>
<td>R2CHADS2</td>
<td>1.9 1.4–2.6 &lt;0.001</td>
<td>1.8 1.3–2.4 &lt;<strong>0.001</strong></td>
<td>_ _ _ _ _ _ _</td>
<td>_ _ _ _ _ _ _</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>1.8 1.3–2.4 &lt;0.001</td>
<td>_ _ _ _ _ _ _</td>
<td>1.7 1.2–2.3 <strong>0.001</strong></td>
<td>_ _ _ _ _ _ _</td>
</tr>
</tbody>
</table>

Abbreviations: UV – univariable analysis, MV – multivariable analysis, PAD – peripheral artery disease, TE – thromboembolic events, RD – renal dysfunction (eGFR <60 ml/min/1.72m²)

**eTable 3.** Clinical predictors for thromboembolic events in patients with AF recurrence (n=402)

<table>
<thead>
<tr>
<th>Variables</th>
<th>UV</th>
<th>MV Model 1</th>
<th>MV Model 2</th>
<th>MV Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI P-value</td>
<td>HR 95% CI P-value</td>
<td>HR 95% CI P-value</td>
<td>HR 95% CI P-value</td>
</tr>
<tr>
<td>PAD</td>
<td>7.4 1.7–32 <strong>0.007</strong></td>
<td>3.5 0.74–16.1 0.114</td>
<td>4.4 0.98–20.2 0.053</td>
<td>_ _ _ _ _ _ _</td>
</tr>
<tr>
<td>Previous TE</td>
<td>5.3 1.3–22.1 <strong>0.023</strong></td>
<td>_ _ _ _ _ _ _</td>
<td>_ _ _ _ _ _ _</td>
<td>_ _ _ _ _ _ _</td>
</tr>
<tr>
<td>RD</td>
<td>3.5 0.7–17.1 0.128</td>
<td>2.2 0.5–9.4 0.304</td>
<td>1.1 1.4–3.4 0.869</td>
<td>_ _ _ _ _ _ _</td>
</tr>
<tr>
<td>CHADS2</td>
<td>2.3 1.4–3.7 <strong>0.001</strong></td>
<td>2.0 1.2–3.3 <strong>0.011</strong></td>
<td>_ _ _ _ _ _ _</td>
<td>_ _ _ _ _ _ _</td>
</tr>
<tr>
<td>R2CHADS2</td>
<td>1.9 1.3–2.8 <strong>0.001</strong></td>
<td>1.8 1.2–2.7 <strong>0.004</strong></td>
<td>_ _ _ _ _ _ _</td>
<td>_ _ _ _ _ _ _</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>2.3 1.5–3.4 &lt;0.001</td>
<td>_ _ _ _ _ _ _</td>
<td>2.2 1.4–3.4 &lt;<strong>0.001</strong></td>
<td>_ _ _ _ _ _ _</td>
</tr>
</tbody>
</table>

Abbreviations: as in eTable 2.
Figure e1. ROC curves for the CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc and R<sub>2</sub>CHADS<sub>2</sub> scores in predicting TE events in patients with AF recurrences (n=402).

Abbreviations as in Figure 1

Significance levels:
- CHADS<sub>2</sub> vs R<sub>2</sub>CHADS<sub>2</sub> \( p = 0.661 \)
- CHADS<sub>2</sub> vs CHA<sub>2</sub>DS<sub>2</sub>-VASc \( p = 0.022 \)
- R<sub>2</sub>CHADS<sub>2</sub> vs CHA<sub>2</sub>DS<sub>2</sub>-VASc \( p = 0.031 \)