Long-term events following atrial fibrillation rate control or transcatheter ablation: a multicenter observational study

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Long-term events following AF rate control or transcatheter ablation. A multicenter observational study.


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Abstract

Background: Atrial fibrillation (AF) increases thromboembolic (TE) risk. Oral anticoagulation with antivitamin K (AVK) reduces TE event rate but increases hemorrhagic risk.

Objective: Aim of the present study is to describe long-term cerebral TE/hemorrhagic event rates in AF patients managed by rhythm control, pursued by AF transcatheter ablation (AFTCA), and rate control strategy.

Methods and Results: 1,500 consecutive patients referring in three medical care centers for AF were retrospectively divided in three groups: AFTCA maintaining AVK (group A); AFTCA discontinuing AVK (group B); rate control strategy and AVK (group C). TE and hemorrhagic events were recorded in 60±28 months follow-up. TE events did not differ between groups (5/500, 1% A; 7/500, 1.4% B; 11/500, 2.2% C, p=0.45), hemorrhagic events were greater in group A (9/500, 1.8%) and C (12/500, 2.4%) than in group B (no events, p=0.003). Among patients with CHA²DS²VASc Ø TE events did not differ in the group discontinuing (B, 4/388, 1%) or not (A, 1/319, 0.3%) AVK (p=0.38), while hemorrhagic events were more common in patients on AVK (5/319, 1.5% A and 3/175, 1.7% C, p=0.02) compared to those discontinuing AVK (0/388, B). Following AFTCA (groups A-B) 299/1000 experienced AF relapses; all TE events (12/299, 4%) occurred within these patients (p < 0.001).

Conclusion: Considering this multicenter design study AVK continuation following AFTCA, especially within patients with low-intermediate TE risk, confers an hemorrhagic risk greater to the TE protective effect. All TE events following
AFTCA occur within patients experiencing AF relapses therefore, in patients with high TE risk routine rhythm monitoring is essential after AVK discontinuation.

**Keywords:** Atrial Fibrillation, oral anticoagulant therapy, thromboembolic event, hemorrhagic event, transcatheter ablation

**Glossary of abbreviations used in the manuscript:** AF, atrial fibrillation; AVK, antivitamin K; TE, thromboembolic event; AFTCA, atrial fibrillation transcatheter ablation.
Introduction

Atrial fibrillation (AF), the most common supraventricular sustained arrhythmia\(^1\), worsens patients\(^\text{\textregistered}\) quality of life and increases, by 5 folds, the risk of stroke\(^2\). In fact, in case AF is documented, anticoagulation, usually oral with antivitamin K (AVK), is recommended in order to reduce thromboembolic event (TE) rate and consequent mortality\(^1\). First guidelines on this topic\(^3\), \(^4\) supported AVK prescription in intermediate-high TE risk patients stratified according to CHADS\(_2\) score \(\geq 2\). The recent introduction of CHA\(_2\)DS\(_2\)VASc score\(^5\) has improved TE risk stratification by detecting the truly low TE risk patients (CHADS\(_2\) 0-1) avoiding unnecessary AVK prescription\(^6\). In fact the benefit obtained with AVK should always be balanced by the related hemorrhagic risk\(^7\), in particular, within patients at low TE risk. Given that sinus rhythm maintenance following AF transcatheter ablation (AFTCA) should represent the ideal clinical solution, how should AVK be managed after the procedure? The latest ESC/AHA \(^1\), \(^8\) guidelines support AVK prescription in all patients the first two-three months after AFTCA (considered as a blanking period) followed by a tailored decision weighted by the individual TE and hemorrhagic risk.

Aim of the present study is to report long-term cerebral TE/hemorrhagic event rates within AF patients managed by AFTCA and rate control strategy.

Methods

In the present observational study we screened consecutive patients affected by AF referred, between 2003 and 2011, to three cardiological centers (Città della Salute e della Scienza Hospital of Turin, Mauriziano Hospital of Turin and Cardinal Massaia Hospital of Asti). Within patients with CHA\(_2\)DS\(_2\)VASc\(^\text{\textregistered}\) weretrospectively described, based on status on May 2014, the first 500 patients for
each of the following groups: patients undergoing AFTCA and not discontinuing AVK (AFTCA+ AVK, group A); patients undergoing AFTCA that, after 3 months, according to physician advice, in absence of AF recurrences and/or with CHA2DS2VASc<3, discontinued AVK (AFCTA, group B); patients managed by rate control strategy and AVK (without antiarrhythmic drugs at the time of enrollment, rate control, group C). AVK daily dosage was routinely supplied by a dedicated center with the aim of reaching a time in therapeutic range > 60%.9. Consecutive patients undergone to either rhythm control strategy pursued by AFTCA or rate control strategy were extracted from an established prospectively maintained database of all centers enrolled accounting for a total of 2710 patients. Based on known recurrence predictors - as longer AF history, AF induced atrial remodeling, underlying valvular or structural cardiomyopathy - transcatheter ablation was not proposed to patients with a low benefit/risk ratio. In addition, patients’ preference was indeed considered. Patients were excluded in case of CHA2DS2VASc equal to 0 or presence of structural cardiomyopathy or AVK indication for reasons other than atrial fibrillation (e.g. mechanical prosthetic heart valve or thrombophilia). Enrolment date was considered the date in which the management strategy was decided and adopted and the follow-up end the last medical contact or ambulatory visits performed. Enrollment was stopped at the reaching of 500 consecutive patients for each group. We considered as a recurrence the presence of a sustained AF/atrial flutter lasting more than 30 seconds either symptomatic or documented by means of ECG or 24 hours Holtermonitoring. The study was performed in accordance to the latest Declaration of Helsinki. The study consisted of anonymous analysis of data collected during routine clinical examination. All the procedures were performed as part of routine care and testing, and not specifically for the purpose of this study.
Clinical events. Cerebral TE event was defined as a neurological deficit, transient or not, with infarction evidence at imaging\textsuperscript{10} (all patients positive for cerebral TE underwent brain imaging both in the acute and post-acute phase together with neurologist\textsuperscript{a} assessment). Major hemorrhagic event was defined, according to the latest International Society on Thrombosis and Hemostasis (ISTH) definition of major bleeding, as a fatal bleeding, and/or symptomatic bleeding in a critical area or organ (such as intracranial or gastrointestinal) and/or bleeding leading to blood transfusion\textsuperscript{11}. In case of any clinical event the patients were recommended to provide complete documentation at the following outpatient visit.

Follow up. In all three groups follow up data was collected since the destination therapy was adopted; for patients in Group C, for example, inclusion in the study started from the date the rate control strategy was pursued, regardless of any previous rhythm control strategy adopted. For patients in Group A and B, instead, from the first AFTCA performed. In fact, enrolment date was always considered the date in which the management strategy was decided and adopted and the follow-up end the last medical contact or ambulatory visits performed. Baseline characteristics of the study population, follow-up data and thromboembolic and hemorrhagic events have retrospectively been recorded at routine outpatient visits performed at 1, 3, 6 months and then yearly following AFTCA in groups A and B and yearly in group C. Twenty-four hours Holter ECG monitoring was performed in all patients every six months.

AF ablation procedure. Procedural details concerning AFTCA performed in group A and B have been reported elsewhere\textsuperscript{12}. In brief, each procedure was performed under conscious sedation and guided by a 3-dimensional reconstruction of the left atrium and pulmonary vein (PV) ostia with the use of electroanatomic mapping
systems, CARTO (Biosense Webster) or Navx (Saint Jude Medical). Paroxysmal AF patients underwent antral pulmonary vein isolation (PVI) and, only in case of redo procedure, linear lesions were performed. In patients with persistent AF a line connecting superior pulmonary veins, a line from left inferior PV to mitralannulus (råde scheme) and complex fragmented atrial electrograms (CFAE) were performed in addition to PVI. Redo procedures were proposed to patients with symptomatic recurrences considering patient’s preference with the aim of reducing AF-related symptoms and improving quality of life.

Statistical analysis. Categorical variables are reported as counts and percentages, while continuous variables as means and standard deviations (SD). Correlations between parameters and study groups were tested in cross tabulation tables by means of the Pearson Chi-Square or Fisher’s Exact Test and by one-way ANOVA respectively for categorical and continuous variables. Kaplan Meier curves were used to describe event free survival over time stratified for study groups and compared by log-rank test. A two sided p-value <0.05 was considered statistically significant; all analyses were performed with SPSS 20.0 (IBM Corp., Armonk, NY, USA).

Results

We retrospectively analyzed 1500 total patients over a mean period of 60 ± 28 months. Forty six patients (3.1%) were lost to follow up. Clinical characteristic did not differ between this subgroup and the other patients. Clinical features of the study population are listed in Table 1. Patients undergoing AFTCA (groups A and B) were generally younger (p<0.001) and presented lower CHA2DS2VASc score (p<0.001) compared to those approached by rate control (group C). Moreover patients treated by AFTCA + AVK (Group A) reported an higher arrhythmia
burden at the time of enrollment due to a higher prevalence of persistent AF and significantly larger left atria dimension (p < 0.05). During the follow-up period 12 (0.31 per 100 patients years) and 9 (0.23 per 100 patients year) patients undergoing AFTCA and in 11 (0.54 per 100 patients year) and 12 (0.58 per 100 patients years) patients in group C reported TE and hemorrhagic events, respectively. Of the 12 TE events that occurred in Group A+B 2 cases lead to death (for the patient in Group A the event occurred 19 months after the procedure while for the patient in Group B the event occurred 7 months after AFTCA), 6 cases presented permanent and 4 transient neurological deficits. Within patients treated by rate control strategy 11 TE events occurred: 9 cases lead to permanent and 2 cases to transient neurological deficits. On the other side hemorrhagic events occurred in 9 patients treated by rhythm control strategy (Group A+B): 1 lead to death, 3 to neurological deficits (one case of which with permanent hemiparesis) and 5 were gastrointestinal bleedings. Hemorrhagic events in Group C lead to one death, 8 cases of neurological deficit (4 of whom with permanent consequences) and 3 gastrointestinal bleedings. TE events (5/500, 0.29 per 100 patients/year in group A; 7/500, 0.33 per 100 patients/year in group B; 11/500, 0.54 per 100 patients/year in group C) did not differ within study groups (p 0.45) while survival free from hemorrhagic events was significantly greater in patients in group B (no events), treated by AFTCA and off AVK (p 0.003) compared to the other two groups (9/500, 1.8% in group A; 12/500, 2.4% in group C; Figure 1). In the time of enrollment oral anticoagulant therapy was performed only using AVK because of unavailability of novel oral anticoagulant. AVK daily dosage was managed by a dedicated centre with the aim of reaching a time in therapeutic range > 60%. Despite different baseline characteristics, stratifying patients for their TE risk, TE event rate within patients with low-intermediate risk did not differ between rate and
rhythm control strategy (CHA2DS2VASe = 1 Group A+B 2/315, 0.63% vs Group C 0/61, 0%, p= 0.701, CHA2DS2VASe = 2 Group A+B 3/392, 0.76% vs Group C 1/114, 0.87%, p=0.464). Moreover no treatment related differences were reported in high TE risk patients (group A+B, 7/293, 2.4% vs. group C 10/325, 3%, p 0.27).

More in details, considering the subgroup of patients treated by rhythm control strategy, TE events, within patients with a low-intermediate risk, did not differ in the group discontinuing or not AVK (CHA2DS2VASe = 1 Group A 0/136, 0% vs Group B 2/179, 1.1%, p= 0.322, CHA2DS2VASe = 2 Group A 1/183, 0.54% vs Group B 2/209, 0.95%, p=0.550). On the other side hemorrhagic events, in patients with CHA2DS2VASe ≤2, were significantly more commonly suffered (p 0.02) in the group of patients on AVK (5/319, 1.5% in group A and 3/175, 1.7% in group C) compared to those discontinuing AVK (0/388 in group B; Figure 2). Within patients undergoing AFTCA (groups A and B) a periprocedural complication has been reported in 28/1000 cases (2.8%). Vascular complication and pericardial tamponade requiring pericardiocentesis were more frequently reported (respectively 9 and 12). A periprocedural stroke was reported in 5 patients (0.5%). During the follow up, within patients undergoing AFTCA, 701/1000, 70% maintained sinus rhythm while 299/1000, 30% experienced at least one AF relapse during the study period. All TE events (12/299, 4%) were recorded within patients suffering AF relapses while none was reported within those maintaining sinus rhythm (p < 0.001). Figure 3 illustrates freedom from TE events within patients maintaining sinus rhythm and those suffering AF relapses with low-intermediate (CHA2DS2VASe score ≤2) or high (CHA2DS2VASe ≥3; p < 0.001).

Discussion
TE events related to AF lead to high mortality rates and/or comorbidity burden. Despite AF suppression, by sinus rhythm maintenance, theoretically should represent the ideal clinical solution, controversial data emerged concerning the long-term effect of rhythm over rate control strategies. Previous trials concluded that rhythm control strategy offers no advantages on TE event rate and total survival. Conversely, De Vos et al16 reported that rhythm control strategy, over a follow-up of one year, prevents AF progression (11% within patients managed by rhythm control vs. 26% within those managed by rate control, p < 0.001), and, interestingly, in the group of patients in which AF progression was not documented a lower incidence of TE events was reported. In this study rhythm control strategy was pursued by AFTCA only in a minority of patients (2%). The aforementioned studies, in fact, may have been influenced by the poor efficacy and frequent side effects of the approaches prescribed, mostly antiarrhythmic drugs, to suppress AF.

The present study population confirms that patients referred to AFTCA are generally younger and present a lower CHA2DS2VASc score compared to those managed by rate control strategy. AFTCA is emerging as a promising therapeutic strategy for AF and the number of the procedures performed worldwide is progressively increasing. In fact, if rhythm control strategy reduces AF burden it is reasonable to assume that this would avoid the "primum movens" leading to TE events and it would candidate as the "best anticoagulant therapy" for AF patients.

How should AVK be then managed after the procedure? Current guidelines recommend AVK prescription, avoiding it only in "truly low" TE risk patients. Following AFTCA, AVK maintenance is recommended for at least two-three months and further treatment tailored on individual TE/hemorrhagic risk. Recent studies, however, based on short-medium term follow-up, suggest a protective...
effect of rhythm control strategy on TE events, also in absence of AVK. Hunter et al 18, on a large cohort of AF patients undergoing AFTCA, concluded that restoration of sinus rhythm related to a reduced TE event rate (stroke free survival after 7 years follow up 97.8% vs 92.7%, p< 0.001) suggesting that anticoagulation may not be necessary, if not harmful, by increasing hemorrhagic events.

Themistoclakis et al19, after a mean follow up of 26 months showed that TE events did not differ between On and Off AVK patients (2, 0.07% Off-AVK vs. 3, 0.45% On-AVK, p value 0.06) while hemorrhagic events were more frequently reported in AVK patients (1, 0.04% Off-AVK vs. 13.2% On-AVK group patients p < 0.0001).

Accordingly, Hunter et al18, on 1273 patients undergoing AFTCA, reported that no TE events occurred in high TE risk patients (CHADS2≥ 2) despite discontinuation of AVK after a three years follow-up. Eventually Hussain et al20, based on a cohort of 831 patients, reported, in the first year of follow-up, a very low TE event rate of 0.06 per 100 patients year by discontinuing AVK after AFTCA in all CHADS2< 3 patients and Oral et al21 reported, after 25 months follow-up, no TE events within 755 AF patients in which AVK was discontinued in case of successful AFTCA, independently by TE risk. In this setting the aim of the present study is not a prospective comparison of rhythm versus rate control strategy but to provide the clinical picture of multicenter clinical practice concerning long-term incidence of TE/hemorrhagic events in a fairly large population. In the present study AVK maintenance did not significantly reduce TE events but increased hemorrhagic risk. This trend was particularly present within low-intermediate baseline TE risk patients (CHA2DS2VASc ≥). Overall, the strongest protector from TE events was, in fact, sinus rhythm maintenance. All TE events reported in our study occurred in patients experiencing AF recurrence. The beneficial effect of AFTCA is also underlined by the lower periprocedural complication rate reported in our study, by
far lower than what reported in literature. Awaiting randomized clinical trials on this topic also including the use of novel oral anticoagulants (that were not available when this study was performed), the present report, together with the aforementioned short-medium term follow-up previous literature support AVK discontinuation following AFTCA, at least within patients with low-intermediate TE risk. In this group of patients, in fact, hemorrhagic risk is significantly greater than the TE protective effect. In fact a better selection of patients at higher TE event risk (by CHA2DS2-Vasc) could help to improve identification of whose who will benefit from AVK. Our data suggests that embolic risk is mostly related to arrhythmic recurrences and therefore we suggest that a strict ECG monitoring could improve management by identifying the frequent asymptomatic recurrences. Eventually recent introduction of novel oral anticoagulants (NAO) has improved thromboembolic risk management. These new drugs reported, in several clinical trials, lower cerebral hemorrhagic rates, one of the worst counterparts of AVK. In case this finding will be confirmed also in everyday clinical practice, oral anticoagulation may indeed be more widely and easily recommended., bearing in mind that clinical use may somewhat be limited by dependency on renal/hepatic excretion and interactions with other commonly prescribed drugs.

**Conclusion**

In the light of our results we support AVK discontinuation following AFTCA in low TE risk patients because of higher hemorrhagic risk than TE risk. Regarding high TE risk patients we suggest AVK discontinuation especially in patients with symptomatic recurrences if a daily rhythm assessment, e.g. by daily pulse detection or pressure measurement devices enabled to detect AF recurrences, may be performed. Whether a strict ECG monitoring could better identify also
asymptomatic recurrences in order to correctly guide NAO or AVK interruption following AF ablation despite different CHA2DS2VASc scores, needs to be confirmed by future large randomized trials.

**Study limitation**

The following limitations must be taken in account. First, this report is a retrospective analysis and not an observational study: stratification in study groups may certainly be biased by patient selection by physician in charge (the three subgroups of the study population are, in fact, not directly comparable). Second, the limited clinical events did not permit multivariate analysis to detect independent inference of the study parameters. Third, in this analysis AVK considered was only warfarin because the new oral anticoagulants were not available during years of study follow-up.

**Acknowledgements:** none

**Conflict of interest:** none to declare

**References**


organized by the German Atrial Fibrillation Competence NETwork (AFNET) and the European Heart Rhythm Association (EHRA). *Eur Heart J* 2007; 28:2803–2817.


6. Chao TF, Lin YJ, Tsao HM et al. CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}VASe scores in the prediction of clinical outcomes in patients with atrial fibrillation after catheter ablation. *J Am CollCardiol* 2011; 58:2380–2385.


recurrences following transcatheter atrial fibrillation ablation. Pacing

ClinElectrophysiol2014;37(6):697-702
Table 1. Baseline characteristics stratified by study groups. Values reported as counts and percentage if not differently stated. P value by Pearson Chi-Square/Fisher’s Exact Test or ANOVA. AF, Atrial Fibrillation; AP, antero-posterior diameter; DM, diabetes mellitus; LA, left atrium; LM, latero-medial diameter; SI, supero-inferior diameter; TE, thromboembolic events.

<table>
<thead>
<tr>
<th></th>
<th>Group A (AFTCA + AVK)</th>
<th>Group B (AFTCA)</th>
<th>P value</th>
<th>Group A + B</th>
<th>Group C (Permanent AF)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.</td>
<td>500</td>
<td>500</td>
<td>&lt;0.001</td>
<td>1000</td>
<td>500</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>64±8</td>
<td>60±10</td>
<td></td>
<td>61±9</td>
<td>70±9</td>
<td></td>
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<tr>
<td>Sex (males)</td>
<td>323 (64.6%)</td>
<td>361 (72.2%)</td>
<td>0.010</td>
<td>684 (68%)</td>
<td>287 (57.4%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Hypertension</td>
<td>377 (75%)</td>
<td>372 (74%)</td>
<td>0.715</td>
<td>749 (75%)</td>
<td>392 (78%)</td>
<td>0.134</td>
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<tr>
<td>DM</td>
<td>47 (9%)</td>
<td>38 (7%)</td>
<td>0.307</td>
<td>85 (8.5%)</td>
<td>93 (18%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Heart Failure</td>
<td>23 (4.6%)</td>
<td>27 (5.4%)</td>
<td></td>
<td>50(5%)</td>
<td>66 (13.2%)</td>
<td></td>
</tr>
<tr>
<td>Vascular disease</td>
<td>65 (13%)</td>
<td>143 (29%)</td>
<td></td>
<td>208(21%)</td>
<td>96 (19.2%)</td>
<td></td>
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<tr>
<td>Mean CHA2DS2VASC (value ± SD)</td>
<td>2,4 ± 1</td>
<td>1,9 ± 0,9</td>
<td></td>
<td>2,1 ± 1,1</td>
<td>3 ± 1,3</td>
<td></td>
</tr>
<tr>
<td>Antiarrhythm drugs Class Ic</td>
<td>343 (69%)</td>
<td>363 (72%)</td>
<td></td>
<td>706 (71%)</td>
<td>310 (62%)</td>
<td></td>
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<tr>
<td>Class III</td>
<td>132 (27%)</td>
<td>183 (36%)</td>
<td></td>
<td>315 (32%)</td>
<td>87 (17%)</td>
<td></td>
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<tr>
<td>Antiplatelet treatment</td>
<td>211 (42%)</td>
<td>180 (36%)</td>
<td></td>
<td>391 (39%)</td>
<td>223 (45%)</td>
<td></td>
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<tr>
<td>Previous TE event</td>
<td>40 (8%)</td>
<td>24 (5%)</td>
<td>0.213</td>
<td>64 (6.4%)</td>
<td>46 (9.2%)</td>
<td>0.782</td>
</tr>
<tr>
<td>AF type</td>
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<td></td>
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<td></td>
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<td></td>
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<tr>
<td>paroxysmal</td>
<td>232(46%)</td>
<td>276(55%)</td>
<td>0.005</td>
<td>508 (51%)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>persistent</td>
<td>268(54%)</td>
<td>224(45%)</td>
<td></td>
<td>492 (49%)</td>
<td></td>
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</tr>
<tr>
<td>LA diameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AP</td>
<td>47 ± 6</td>
<td>45 ± 6</td>
<td>0.059</td>
<td>45 ± 6</td>
<td>49 ± 7</td>
<td>&lt;0.001</td>
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<tr>
<td>LM</td>
<td>48 ± 8</td>
<td>46 ± 8</td>
<td>0.352</td>
<td>47 ± 8</td>
<td>51 ± 7</td>
<td>0.004</td>
</tr>
<tr>
<td>SI</td>
<td>62 ± 8</td>
<td>59 ± 7</td>
<td>&lt;0.001</td>
<td>60 ± 8</td>
<td>68 ± 7</td>
<td>&lt;0.001</td>
</tr>
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</table>
Table 2. Detailed thromboembolic and hemorrhagic risk profile according to group assignment

<table>
<thead>
<tr>
<th>Score</th>
<th>Group A (AFTCA + AVK)</th>
<th>Group B (AFTCA)</th>
<th>Group C (Permanent AF)</th>
</tr>
</thead>
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<tr>
<td>ChadsVasc score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>136 (27.2%)</td>
<td>179 (35.8%)</td>
<td>61 (12.2%)</td>
</tr>
<tr>
<td>2</td>
<td>183 (36.6%)</td>
<td>209 (41.8%)</td>
<td>114 (22.8%)</td>
</tr>
<tr>
<td>≥3</td>
<td>181 (36.2%)</td>
<td>112 (22.4%)</td>
<td>325 (65%)</td>
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<td>HASBLED score</td>
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<td></td>
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<tr>
<td>0</td>
<td>46 (9.2%)</td>
<td>96 (19.2%)</td>
<td>18 (3.6%)</td>
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<tr>
<td>1</td>
<td>199 (39.8%)</td>
<td>282 (56.4%)</td>
<td>162 (32.4%)</td>
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<tr>
<td>2</td>
<td>204 (40.8%)</td>
<td>105 (20.4%)</td>
<td>271 (54.2%)</td>
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<tr>
<td>≥3</td>
<td>51 (10.2%)</td>
<td>17 (3.4%)</td>
<td>49 (9.8%)</td>
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</tbody>
</table>
**Figure legends**

**Figure 1.** Kaplan Meier curves for event free survival from thromboembolic (left) and hemorrhagic (right) events stratified by study groups (group A continuous line, group B dotted line, group C traced line). P value by log-rank test.

**Figure 2.** Clinical events (thromboembolic, white bars; hemorrhagic, grey bars) during the 60 months follow-up stratified by study groups and CHA$_2$DS$_2$VASc score. Values reported as counts and percentage if not differently stated. In the brackets are reported patients in sinus rhythm of each group. SR, sinus rhythm, TE, thromboembolic events.

**Figure 3.** Kaplan Meier curves for event free survival from thromboembolic events comparing patients maintaining sinus rhythm (dotted line) and those suffering relapses with CHA$_2$DS$_2$VASc score $\leq 2$ (continuous line) and $\geq 3$ (traced line). P value by log-rank test.
Figure 2.

Figure 3.
Event-free survival from thromboembolic event

Log rank P value < 0.001

- Sinus rhythm
- AF with CHA₂DS₂-VASc ≤ 2
- AF with CHA₂DS₂-VASc ≥ 3
- AF with CHA₂DS₂-VASc

Patients at risk

<table>
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<th>Follow-up (months)</th>
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<td>AF with CHA₂DS₂-VASc ≥ 3</td>
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