Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation?

Robby Nieuwlaat1*, Trang Dinh1, S. Bertil Olsson2, A. John Camm3, Alessandro Capucci4, Robert G. Tieleman1, Gregory Y.H. Lip5, and Harry J.G.M. Crijns1 on behalf of the Euro Heart Survey Investigators

1Department of Cardiology, University Hospital Maastricht, P. Debyelaan 25, PO Box 5800, Maastricht 6221AZ, The Netherlands; 2Department of Cardiology, University Hospital Lund, Lund, Sweden; 3Department of Cardiology, St George’s Hospital, London, UK; 4Department of Cardiology, Guglielmo da Saliceto Hospital, Piacenza, Italy; and 5Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, UK

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Aims
To assess the relation between the atrial fibrillation (AF) subtype and thrombo-embolic events.

Methods and results
The observational Euro Heart Survey on AF (2003–04) enrolled 1509 paroxysmal, 1109 persistent, and 1515 permanent AF patients, according to the 2001 American College of Cardiology, American Heart Association, and the European Society of Cardiology guidelines definitions. A 1 year follow-up was performed. Permanent AF patients had at baseline a worse stroke risk profile than paroxysmal and persistent AF patients. In paroxysmal AF, the risk for stroke, any thrombo-embolism, major bleeding and the combined endpoint of cardiovascular mortality, any thrombo-embolism, and major bleeding was comparable with persistent and permanent AF, in both univariable and multivariable analyses. Compared with AF patients without stroke, patients suffering from a stroke had a comparable frequency and duration of AF attacks, but tended to have a worse stroke risk profile at baseline. During 1 year following cardioversion, paroxysmal AF patients had a higher risk for stroke (P = 0.029) and any thrombo-embolism (P = 0.001) than persistent AF patients.

Conclusion
In the Euro Heart Survey, paroxysmal AF had a comparable risk for thrombo-embolic events as persistent and permanent AF. This observation strengthens the guideline recommendation not to consider the clinical AF subtype when deciding on anticoagulation.

Keywords
Atrial fibrillation • Subtype • Paroxysmal atrial fibrillation • Stroke • Thrombo-embolism • Anticoagulation

Introduction
The Euro Heart Survey on atrial fibrillation (AF), and also the NABOR programme, reported that contemporary paroxysmal AF patients had a lower chance for receiving oral anticoagulation (OAC) than persistent and permanent AF patients.1,2 This observation probably relates to the traditional paradigm that anticoagulation is considered less essential with short and infrequent AF episodes. However, no clear evidence exists regarding the effect of AF duration and frequency on occurrence of stroke. Is a single, long-lasting AF episode alarming? It seems plausible that a long AF duration increases the risk for thrombus formation. Furthermore, frequent ‘stopping and starting’ of AF might be of concern, given the cluster of thrombo-embolism around rhythm transition.3 Stroke risk is also increased directly after restoration of sinus rhythm, probably because of the mechanism of atrial stunning, which might also increase stroke risk in paroxysmal AF with frequent episodes that terminate spontaneously.4 However, regardless of the significance of the duration and frequency of AF episodes, it is quite hard in daily practice to measure these variables exactly since asymptomatic episodes or periods are common.5 Thus, we rely on the clinical subtype of AF to estimate...
the effect of AF duration and frequency on stroke risk. Some studies have suggested a lower stroke risk in paroxysmal than in persistent AF.\textsuperscript{6,7} In contrast, other studies have reported a comparable stroke risk of paroxysmal to permanent AF.\textsuperscript{8} The largest data set is the pooled analysis of aspirin-treated paroxysmal AF subjects in the SPAF trials, which concluded that the risk of stroke in intermittent (paroxysmal) AF was comparable with permanent AF.\textsuperscript{8} Consequently, the 2006 guidelines of the American College of Cardiology (ACC), American Heart Association (AHA), and the European Society of Cardiology (ESC) on AF management dissuade decisions on antithrombotic treatment by clinical subtype of AF and imply paroxysmal AF subjects should be treated similarly to persistent and permanent AF.\textsuperscript{9}

In order to gain further insight into this issue, we report follow-up data of the Euro Heart Survey on AF, which is the first prospective observational survey to report incidence of thrombo-embolic events in relation to the ACC/AHA/ESC classification of AF type.

**Methods**

In the Euro Heart Survey on AF (2003–04), hospitalized and ambulant AF patients who had AF at enrolment or had an electrocardiogram or Holter monitor showing AF in the preceding 12 months were included in this multinational survey, sponsored by the ESC. Overall, 1509 paroxysmal, 1109 persistent, and 1515 permanent AF patients were enrolled. First detected AF patients were excluded from this analysis, since AF characteristics and temporal pattern were not sufficiently investigated or defined. Survey methods and baseline characteristics have been previously described.\textsuperscript{10}

Definitions of the AF clinical subtypes were consistent with the 2001 ACC/AHA/ESC guidelines\textsuperscript{11} which were in existence at the time of the survey, as follows.

(i) Paroxysmal AF. Recurrent AF that terminates spontaneously and lasts <7 days (mostly <24 h). Termination of AF by pharmacological therapy or electrical cardioversion does not change the designation. In other words, cardioversion does not necessarily differentiate between paroxysmal and persistent AF since pharmacological and electrical cardioversion are used in both conditions;

(ii) Persistent AF. Recurrent AF or sustained AF lasting >7 days;

(iii) Permanent AF. AF which has been present for a long time, cardioversion has not been indicated or used, or one or several attempts have failed to restore reliable sinus rhythm.

The CHADS\textsubscript{2} stroke risk score is an acronym for Congestive heart failure, Hypertension, Age >75 years, Diabetes and prior Stroke/TIA. These factors produce a sum score ranging from 0 to 6 whereby a prior stroke/TIA receives 2 points and the other factors 1 point. The score is based on stroke risk scores of the Stroke Prevention in AF and Atrial Fibrillation Investigators trials and has been validated in a cohort of the National Registry on AF.\textsuperscript{12}

**Assessment of outcome during 1 year follow-up**

In the preparation phase of the survey, a follow-up was planned at 1 year following the baseline survey. Data were collected through searching medical records and patient interview. Using a validation plan, integrated in the data entry software, data were checked for missing or contradictory entries and values out of the normal range. Additional edit checks were performed by the EHS staff at the European Heart House and by the EHS-AF data analysis centre at the University Hospital Maastricht. Further, data consistency was pursued by providing the following standard endpoint data definitions:

- **Stroke** was defined as a focal neurological deficit of sudden onset as diagnosed by a neurologist, lasting >24 h and caused by ischaemia.
- **Any thrombo-embolism** was defined as the occurrence of ischaemic stroke, myocardial infarction, pulmonary embolism, or peripheral embolism.
- **Myocardial infarction** was defined as new or presumed new ST-segment elevation in two or more continuous leads of 0.2 mV in leads V1, V2, or V3 and 0.1 mV in other leads and/or presumed new left bundle branch block and/or cardiac enzyme rise more than twice the upper values.
- **Peripheral embolism** was defined as embolism outside the heart, brain, eyes, and lungs.
- **Cardiovascular mortality** was defined as death due to any cardiovascular reason such as myocardial infarction, heart failure, sudden cardiac death (all sudden deaths without any other known reason), stroke, or rupture of an aortic aneurysm.

We had 1 year follow-up data available for 80% of the baseline population with paroxysmal, persistent, or permanent AF. The median (25–75th percentile) follow-up duration was 380 (366–421) days. Compared with patients with follow-up data available, patients lost to follow-up more often had heart failure (45 vs. 34%; \(P < 0.001\)) and less often received OAC (57 vs. 71%; \(P < 0.001\)). Paroxysmal AF patients were equally often lost to follow-up as persistent and permanent AF patients (20 vs. 21 vs. 19%, respectively; \(P = 0.438\)).

**Cardioversions**

A substantial number of paroxysmal and persistent AF patients underwent pharmacological or electrical cardioversion at the time of the baseline survey. In order to assess whether paroxysmal AF has a comparable risk for thrombo-embolism following these procedures, antithrombotic therapy at discharge and thrombo-embolic event rates during 1 year are reported for paroxysmal and persistent AF patients undergoing cardioversion. Since few permanent AF patients underwent pharmacological (\(n = 41; 3.3\%\)) or electrical cardioversion (\(n = 69; 5\%\))—which is inherent in the definition of permanent AF—and only one of these patients had a thrombo-embolic event, we did not take into account permanent AF in this subanalysis.

**Statistics**

Data analysis was performed with SPSS statistical software (SPSS Inc., release 12.01). Continuous variables are reported as mean ± standard deviation and categorical variables as observed number (percentage within AF subtype). For some variables in Table 4, data availability was limited. Beneath Table 4 we report the exact proportion of data available when the information was available in >90% of patients. Whether there was any difference among the three AF subtypes was tested with either Kruskal–Wallis or one-way ANOVA for continuous variables and with \(\chi^2\) statistic for categorical variables. All tests were two-sided.

Multivariable logistic regression was performed to assess the independent effect of AF subtype on incidence of stroke, any thrombo-embolism, major bleeding and the combined endpoint of cardiovascular mortality, any thrombo-embolism, and major bleeding. AF subtype was put in the model together with well-known or suspected covariates for each of these four endpoints. Potential confounders...
that were taken into account regarding the effect of AF subtype on the occurrence of stroke were age, gender, coronary artery disease, valvular heart disease, hypertension, diabetes, heart failure, prior stroke/TIA, prior other thrombo-embolism, and the use of OAC and antiplatelet drugs. In addition to these factors, peripheral vascular disease and hyperlipidaemia were added to the model regarding the occurrence of any thrombo-embolism. Covariates that were taken into account in assessing the effect of AF subtype on the occurrence of a major bleeding were age, gender, hypertension, prior stroke/TIA, prior major bleeding, renal failure, malignancy, prior minor bleeding, and the use of OAC and antiplatelet drugs. For the analysis on the combined endpoint of cardiovascular mortality, any thrombo-embolism, and major bleeding, all aforementioned variables were incorporated as covariates, with the addition of COPD, sick sinus syndrome, hyperthyroidism, ventricular tachycardia, ventricular fibrillation, sinus rhythm at end of visit, and the use of a rate/rhythm control strategy, beta-blocker, ACE-inhibitor, AT II receptor blocker, and statin. The linearity of the effect of age on all four multivariable analyses endpoints was tested and linearity was in all instances assumed. Results on all four analyses are reported only for the effect of AF subtype, since this comprised the main aim of these analyses.

**Results**

Permanent AF patients were older and more often had a previous stroke, diabetes, and heart failure (all $P < 0.001$) (Table 1). As a consequence, permanent AF patients most often were at the highest risk for stroke according to the CHADS2 score (Figure 1). Regardless of the CHADS2 stroke risk score, paroxysmal AF patients had a much lower chance for receiving OAC at baseline (Table 1, Figure 2).

### Baseline characteristics and management of patients with paroxysmal, persistent, and permanent atrial fibrillation

<table>
<thead>
<tr>
<th>Patient characteristics, n (%)</th>
<th>Paroxysmal AF (n = 1509)</th>
<th>Persistent AF (n = 1109)</th>
<th>Permanent AF (n = 1515)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64 ± 13</td>
<td>66 ± 12</td>
<td>71 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>652 (43)</td>
<td>451 (39)</td>
<td>668 (43)</td>
<td>0.028</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>64 (4)</td>
<td>51 (4)</td>
<td>135 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior transient ischaemic attack</td>
<td>83 (6)</td>
<td>56 (5)</td>
<td>98 (6)</td>
<td>0.222</td>
</tr>
<tr>
<td>Mitral stenosis/valve surgery</td>
<td>96 (6)</td>
<td>113 (10)</td>
<td>279 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>342 (23)</td>
<td>401 (35)</td>
<td>757 (49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>942 (62)</td>
<td>772 (66)</td>
<td>984 (64)</td>
<td>0.078</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>514 (34)</td>
<td>338 (29)</td>
<td>543 (36)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>232 (15)</td>
<td>186 (16)</td>
<td>336 (22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discharge drug therapy, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAC</td>
<td>746 (51)</td>
<td>902 (80)</td>
<td>1143 (76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>538 (36)</td>
<td>238 (21)</td>
<td>385 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any type of antiplatelet agent</td>
<td>603 (40)</td>
<td>256 (22)</td>
<td>428 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heparin</td>
<td>75 (5)</td>
<td>57 (5)</td>
<td>85 (6)</td>
<td>0.704</td>
</tr>
<tr>
<td>No antithrombotic therapy</td>
<td>184 (12)</td>
<td>47 (4)</td>
<td>69 (5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Age is reported as mean ± standard deviation and all other variables as observed number (percentage within AF type). OAC, oral anticoagulation. Data were previously published by Nieuwlaat et al.10

**Effect of clinical atrial fibrillation subtype on cardiovascular outcomes**

During 1 year follow-up, the incidence of stroke was comparable among AF subtypes (Table 2). Cardiovascular mortality and other types of major bleedings than haemorrhagic stroke were most often observed in permanent AF. When adjusting for covariates in multivariable logistic regression, persistent AF had a non-significant lower risk for stroke, any thrombo-embolism, major bleeding and also the combined endpoint of cardiovascular death, any thrombo-embolism, and major bleeding, compared with paroxysmal AF (Table 3, Figure 3). In the same analyses, permanent AF had a non-significant lower risk for stroke and any thrombo-embolism, a non-significant higher risk for major bleeding and a comparable risk for the combined endpoint as compared to paroxysmal AF.

**Characteristics of atrial fibrillation patients with stroke vs. without stroke**

The presence of AF on the ECG at inclusion into the survey tended to be higher prevalent in paroxysmal AF patients who suffered a stroke during follow-up compared with stroke-free patients (Table 4). The latter was however not observed among persistent AF patients. The proportions with an average duration of AF episodes of $>48$ h and with infrequent (yearly) symptomatic episodes were comparable between patients with and without stroke. On the other hand, paroxysmal and persistent AF patients who suffered from a stroke in the preceding year were more often in AF at 1 year and had often had progressed to permanent AF ($P = 0.001$). OAC prescription at baseline was comparable among AF subtypes, although it tended to be lower in persistent
and permanent AF patients suffering from a stroke. Finally, at baseline, paroxysmal AF patients with a stroke were more often at high risk for stroke, i.e. CHADS2 score $\geq 1$, than patients without a stroke. The latter was also observed among persistent and permanent AF patients, although not significant.

**Thrombo-embolic complications associated with cardioversion in paroxysmal and persistent atrial fibrillation**

In the Euro Heart Survey, 496 paroxysmal and 213 persistent AF patients underwent pharmacological cardioversion, and 216 paroxysmal and 424 persistent AF patients underwent electrical cardioversion at baseline. Following pharmacological cardioversion, less paroxysmal AF patients received OAC (41 vs. 64%; $P < 0.001$), but more received aspirin (42 vs. 31%; $P = 0.006$) compared with persistent AF. Following electrical cardioversion, the same was observed for OAC (72 vs. 92%; $P < 0.001$) and aspirin (23 vs. 13%; $P = 0.002$). When paroxysmal was compared with persistent AF, stroke incidence was non-significantly higher in paroxysmal AF during 1 year following both pharmacological (2.6 vs. 0.7%; $P = 0.155$) and electrical cardioversion (1.7 vs. 0.6%; $P = 0.248$), and the incidence of any thrombo-embolism was higher in paroxysmal AF after pharmacological (4.7 vs. 1.3%; $P = 0.069$) and electrical cardioversion (3.7 vs. 0.7%; $P = 0.024$). Taking all cardioversions together, the incidence of stroke and any thrombo-embolism was significantly higher in paroxysmal than in persistent AF (Figure 4).

During follow-up, paroxysmal AF patients more often underwent pharmacological cardioversion (33 vs. 18%; $P < 0.001$) and less often electrical cardioversion (21 vs. 29%; $P = 0.004$) compared with persistent AF. Paroxysmal AF patients less often received OAC than persistent AF after both pharmacological (41 vs. 64%; $P < 0.001$) and electrical cardioversion (72 vs. 92%; $P < 0.001$). The increased thrombo-embolism rates in paroxysmal AF when compared with persistent AF seemed to be present in both patients on OAC (stroke: 2.5 vs. 0.8%; $P = 0.100$ and any thrombo-embolism: 3.7 vs. 0.8%; $P = 0.012$) and off OAC (stroke: 2.7 vs. 0.0%; $P = 0.161$ and any thrombo-embolism: 5.4 vs. 1.4%; $P = 0.153$). When assessing the independent effect of AF subtype on outcome after baseline cardioversion in multivariable logistic regression, thereby taking into account differences in stroke risk profile and antithrombotic therapy, paroxysmal AF still had a higher risk for stroke [OR $= 4.38$ (1.21–15.91); $P = 0.012$] and any thrombo-embolism [OR $= 5.93$ (2.00–17.57); $P < 0.001$] than persistent AF.

**Discussion**

The Euro Heart Survey provides valuable observational prospective clinical practice data on the incidence of stroke related to AF subtype. Although no causal conclusions can be drawn from these data, the results do seem to point towards an at least comparable risk for stroke in paroxysmal AF compared with persistent and permanent AF.

**Clinical subtype of atrial fibrillation**

Several co-morbidities are directly associated with an increased risk for stroke in AF, of which valvular AF is undisputed, and other factors increasing stroke risk in non-valvular AF are brought together in the risk calculation score CHADS2 (congestive heart failure, hypertension, age $\geq 75$ years, diabetes, and prior stroke or TIA). On the basis of these well-known stroke risk factors, the 2006 guidelines provide recommendations for antithrombotic treatment, and they also explicitly state that AF subtype should not influence the management decision. However, evidence on chronic AF being a stroke risk factor when compared with paroxysmal AF is not consistent.

Assessment of stroke risk in relation to clinical subtype of AF depends highly on the definition used for paroxysmal AF, which tends to vary across studies. On the basis of current guideline definitions, the results of the Euro Heart Survey strengthen the recommendation not to take into account the clinical subtype of AF. The risk for stroke might even be higher in paroxysmal AF, as seen after baseline cardioversion in this study. This might relate to the lower OAC application rates in paroxysmal AF after both pharmacological and electrical cardioversions, although the increased thrombo-embolism rate tended to be present in both patients on and off OAC. Potentially, the intermittent
ment have also not yet convincingly revealed a different stroke risk
Current qualitative and quantitative methods of stroke risk assess-
quantitative methods
Potential of current qualitative and
control in the randomized studies.16
the reasons why no advantage was observed with rhythm
by creating intermittent (‘in-and-out’) AF, and this may be one of
versions as used in rhythm control strategies may be thrombogenic
longstanding AF episodes as in persistent AF. Repeated cardio-
nature of paroxysmal AF may be more thrombogenic than single,
longstanding AF episodes as in persistent AF. Repeated cardio-
versions as used in rhythm control strategies may be thrombogenic
by creating intermittent (‘in-and-out’) AF, and this may be one of
the reasons why no advantage was observed with rhythm
control in the randomized studies.16

Potential of current qualitative and quantitative methods
Current qualitative and quantitative methods of stroke risk assess-
ment have also not yet convincingly revealed a different stroke risk
in paroxysmal and persistent/permanent AF. Transoesophageal
echocardiography abnormalities (e.g. spontaneous echo-contrast),
abnormal haemostasis, and reduced local blood flow velocities in
the left atrium contribute to thrombogenesis in AF—and these
have also been found to be present in paroxysmal AF. For
example, abnormal coagulation, platelet aggregation, endothelial
dysfunction, and inflammation are elevated in AF and have also
been shown in paroxysmal AF.17,18 Future prospective clinical
studies could clarify the causal relation between duration and fre-
quency of AF episodes, blood markers, and stroke incidence.

The difficulty with measuring ‘true’ duration and frequency of atrial fibrillation episodes
Although it does seem plausible that long and frequent AF epi-

dose is asymptomatic and will not be reported.5 In
addition, in case of symptomatic attacks, the accuracy of reporting
attacks depends on the patient’s memory and capacity to distin-

Table 2  Major adverse events during 1 year follow-up in patients with paroxysmal, persistent, and permanent atrial fibrillation

<table>
<thead>
<tr>
<th>Major adverse events</th>
<th>Paroxysmal (n = 1170), n (%)</th>
<th>Persistent (n = 886), n (%)</th>
<th>Permanent (n = 1126), n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>43 (3.5)</td>
<td>27 (3.0)</td>
<td>100 (8.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>15 (1.3)</td>
<td>19 (2.1)</td>
<td>43 (3.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Any thrombo-embolism*</td>
<td>37 (3.3)</td>
<td>16 (1.8)</td>
<td>39 (3.3)</td>
<td>0.089</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>22 (1.9)</td>
<td>11 (1.2)</td>
<td>19 (1.6)</td>
<td>0.582</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>3 (0.3)</td>
<td>1 (0.1)</td>
<td>4 (0.3)</td>
<td>0.592</td>
</tr>
<tr>
<td>Other major bleeding</td>
<td>13 (1.1)</td>
<td>7 (0.8)</td>
<td>29 (2.5)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Results are reported as observed number (percentage within AF type).
*Stroke, myocardial infarction, pulmonary embolism, or peripheral embolism. Data are from a manuscript that is provisionally accepted by this journal.

Table 3  The multivariable effect of atrial fibrillation subtype on occurrence of stroke, any thrombo-embolism, major bleeding and the combined endpoint of cardiovascular death, any thrombo-embolism, and major bleeding

<table>
<thead>
<tr>
<th>Major adverse events</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent AF</td>
<td>0.68</td>
<td>0.32–1.46</td>
<td>0.483</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>0.69</td>
<td>0.34–1.38</td>
<td></td>
</tr>
<tr>
<td>Any thrombo-embolism*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent AF</td>
<td>0.65</td>
<td>0.35–1.21</td>
<td>0.374</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>0.87</td>
<td>0.51–1.47</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent AF</td>
<td>0.50</td>
<td>0.20–1.25</td>
<td>0.064</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>1.27</td>
<td>0.66–2.47</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death, any thrombo-embolism, or major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent AF</td>
<td>0.69</td>
<td>0.42–1.16</td>
<td>0.254</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>1.03</td>
<td>0.62–1.71</td>
<td></td>
</tr>
</tbody>
</table>

The effects (odds ratio and 95% confidence interval) of persistent and permanent AF are reported compared with the reference group with paroxysmal AF (odds ratio = 1). The P-value refers to the overall effect of AF subtype in each multivariable outcome analysis. All covariates that were incorporated in each multivariable outcome analysis are summarized in the Methods section. These results are illustrated in Figure 3.
Future perspectives

Upcoming trials such as the TRENDS and the ASSERT studies will provide further insight into the direct relation of AF duration and systemic embolisms in a large group of patients with an implantable device. If these studies confirm the findings of Capucci et al. that a long AF duration increases risk for systemic embolism, the challenge is to measure AF duration in a non-invasive manner and to confirm this relation in a wider spectrum of AF patients. In this regard, the event-loop recorders are promising. When appropriate clinical, quantifiable variables are identified to assess the effect of arrhythmia characteristics on stroke risk and adequate non-invasive monitoring tools are available, it will be

Figure 3 Multivariable effect of atrial fibrillation subtype on outcomes. Results are reported as odds ratio with 95% confidence interval for persistent and permanent atrial fibrillation, compared with the reference group with paroxysmal atrial fibrillation (odds ratio = 1). An odds ratio <1 indicates a lower likelihood and odds ratio >1 a higher likelihood for occurrence of the outcome event.

Table 4 Characteristics of paroxysmal, persistent and permanent atrial fibrillation patients with stroke vs. without a stroke during 1 year follow-up

<table>
<thead>
<tr>
<th></th>
<th>Paroxysmal AF (n = 22)</th>
<th>Persistent AF (n = 11)</th>
<th>Permanent AF (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In AF</td>
<td>16 (73)</td>
<td>8 (73)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Duration of current episode &gt;48 h⁴</td>
<td>11 (54)</td>
<td>412 (58)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>CHADS2 score &gt;1</td>
<td>13 (65)</td>
<td>370 (37)</td>
<td>13 (68)</td>
</tr>
<tr>
<td>OAC</td>
<td>13 (59)</td>
<td>570 (53)</td>
<td>13 (68)</td>
</tr>
<tr>
<td><strong>No stroke</strong></td>
<td>589 (53)</td>
<td>641 (74)</td>
<td>1115 (96)</td>
</tr>
<tr>
<td>Duration of current episode &gt;48 h⁴</td>
<td>412 (58)</td>
<td>677 (87)</td>
<td>332 (87)</td>
</tr>
<tr>
<td>CHADS2 score &gt;1</td>
<td>370 (37)</td>
<td>344 (45)</td>
<td>682 (60)</td>
</tr>
<tr>
<td>OAC</td>
<td>570 (53)</td>
<td>694 (82)</td>
<td>919 (80)</td>
</tr>
<tr>
<td><strong>1 year follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In AF</td>
<td>174 (17)</td>
<td>368 (45)</td>
<td>975 (92)</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>84 (8)</td>
<td>244 (29)</td>
<td>1051 (95)</td>
</tr>
</tbody>
</table>

Time since AF diagnosis is reported as median (25–75th percentile) and all other variables as observed number (percentage within column). CHADS2, acronym for Congestive heart failure, Hypertension, Age >75 years, Diabetes, prior Stroke/TIA.

⁴5% data availability.
⁵62% data availability.
⁶78% data availability.
⁷45% data availability.
Assessing the relation between AF subtype and thrombo-embolic events

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essential to address this important issue in high-quality clinical trials.

Strengths and limitations
The Euro Heart Survey provides unique observational data on stroke incidence in relation to the total spectrum of AF subtypes as seen in European cardiology practice.

We only had estimates, not quantitative information, of the frequency and duration of symptomatic AF episodes. Classification of the clinical subtype of AF and estimation of AF duration and frequency of AF attacks solely relied on the attending physician’s interpretation. We might have underestimated event rates during follow-up, since patients lost to follow-up more often had heart failure and less often received OAC, but there was no bias in this regard related to AF subtype. Unfortunately, we knew only the exact timing of mortality during follow-up and not of the other events. The high proportions of missing data in Table 4 on items concerning the duration and frequency of AF episodes might relate to the fact that these items are often hard to quantify, or they are simply not checked or adequately registered. The incompleteness of these data warrants caution with drawing conclusions. Finally, for patients on OAC, we did not have information on the time spent within or outside the therapeutic INR range—also not at the time of a stroke—and whether OAC was stopped and re-started between the baseline visit and 1 year follow-up.

Conclusions
The results of the EHS-AF indicate that risk for stroke in paroxysmal AF is at least comparable with that of persistent and permanent AF and potentially even higher following cardioversion. These findings strengthen the recommendation that in the presence of appropriate risk factors, clinical subtype of AF, as defined by the ACC/AHA/ESC management guidelines, should currently not influence the decision to anticoagulate. Therefore, we should at present abandon the paradigm that in paroxysmal AF patients anticoagulation may usually be withheld.

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References

Figure 4 Thrombo-embolic complications during 1 year after baseline cardioversion in paroxysmal and persistent atrial fibrillation.

Table 4

![Figure 4](image-url)


