Improved Late Survival and Disability After Stroke With Therapeutic Anticoagulation for Atrial Fibrillation

A Population Study

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Background and Purpose—Although therapeutic anticoagulation improves early (within 1 month) outcomes after ischemic stroke in hospital-admitted patients with atrial fibrillation, no information exists on late outcomes in unselected population-based studies, including patients with all stroke (ischemic and hemorrhagic).

Methods—We identified patients with atrial fibrillation and stroke in a prospective, population-based study in North Dublin. Clinical characteristics, stroke subtype, stroke severity (National Institutes of Health Stroke Scale), prestroke antithrombotic medication, and International Normalized Ratio (INR) at onset were documented. Modified Rankin Scale (mRS) score was measured before stroke and at 7, 28, and 90 days; 1 year; and 2 years after stroke.

Results—One hundred seventy-five patients had atrial fibrillation–associated stroke and medication data at stroke onset (159 ischemic, 16 hemorrhagic); 17% of those with ischemic stroke were anticoagulated before stroke (27 of 159). On multivariable analysis, therapeutic INR was associated with improved late survival after ischemic stroke (adjusted 2-year odds ratio for death=0.08; 95% CI, 0.01 to 0.78; P=0.03). This survival benefit persisted when patients with hemorrhagic stroke were included (2-year survival; 70.5% therapeutic INR, 43.3% nontherapeutic INR; log-rank P<0.001; odds ratio for death=0.27; 95% CI, 0.09 to 0.88; P=0.03). Admission INR was inversely correlated with early and late modified Rankin Scale score (2-year Spearman ρ=−0.65; P<0.0003). An INR of 2 to 3 at ischemic stroke onset was associated with greater early (72 hours to 28 days) modified Rankin Scale score improvement (P=0.04) and good functional outcome (modified Rankin Scale score=0 to 2) at 1 year (adjusted odds ratio=4.8; 95% CI, 1.45 to 23.8; P=0.04).

Conclusions—In addition to improving short-term outcome in selected hospital-treated patient groups, therapeutic anticoagulation may provide important benefits for long-term stroke outcomes in unselected populations. (Stroke. 2011; 42:2503-2508.)

Key Words: atrial fibrillation ▪ stroke prevention ▪ anticoagulation

Atrial fibrillation (AF) is independently associated with a 5-fold increase in risk for ischemic stroke.1 The proportion of stroke associated with AF increases with age, ranging from 6.7% in individuals age 50 to 59 to 36.2% in those age 80 to 89 years.2 With increasing life expectancy, the prevalence of AF is projected to increase 2.5-fold by 2050, with a consequent likely increase in the prevalence of AF-attributable stroke.3 Patients with AF-associated stroke have greater neurologic impairment, worse disability, higher mortality, and more frequent stroke recurrences compared with those without AF.4–6 AF-associated stroke also contributes substantially to the economic burden of stroke, owing to prolonged hospitalizations and greater dependency after discharge.7

Adjusted-dose warfarin to achieve an International Normalized Ratio (INR) of 2 to 3 reduces stroke risk by ≈60% in patients with nonvalvular AF.8 Hospital-based studies and health insurance data indicate that therapeutic anticoagulation at stroke onset is also associated with improved short-term disability at hospital discharge.9–12 However, little informa-

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tion exists on the relationship between antithrombotic therapy at stroke onset and long-term disability and fatality after ischemic stroke. It is important to determine late outcomes for 2 reasons. First, improved outcome may not be apparent in some patients at hospital discharge or at 28 days and may only be observed at late follow-up. Second, it is possible that the early benefit observed in some patients at early follow-up may not be sustained owing to factors such as recurrent stroke, deconditioning after rehabilitation, or comorbid disease.

Although providing valuable insights, studies of hospital registries and health insurance databases may be limited by factors such as selection bias and retrospective design. Few data exist on the overall influence of therapy on outcome when hemorrhagic stroke is also taken into account, which is of primary interest to patients and physicians when deciding to initiate treatment. Prospective population-based studies with extended follow-up are needed to fully determine the relation between antithrombotic therapy and stroke outcome in unselected patients treated in hospital and community settings.

We hypothesized that, in addition to improved early outcomes, therapeutic anticoagulation (INR 2 to 3) would be associated with improved late disability and reduced fatality in patients with all stroke (ischemic and hemorrhagic) and those with ischemic stroke only. We investigated this hypothesis in the population-based North Dublin Population Stroke Study.

Methods

Case Ascertainment

The North Dublin Population Stroke Study is a population-based, prospective study of stroke and transient ischemic attack in North Dublin city (population of 294,529). We ascertained all patients with new stroke events during a 1-year period (December 1, 2005, to November 30, 2006). Ascertainment included “hot” and “cold” pursuit by using multiple overlapping hospital and community sources, according to recommended criteria for rigorous epidemiologic studies (Supplemental Methods, http://stroke.ahajournals.org).

A standardized case-report form was used for documentation of key data variables. An in-person stroke-specialist assessment was performed when stroke/transient ischemic attack status was uncertain. Prestroke function was rated according to the modified Rankin Scale (mRS), with the mRS assessment repeated at 72 hours and at 7 days and the National Institutes of Health Stroke Scale (NIHSS) measured at <72 hours by trained study staff.

Medication use (at onset and discharge) was determined by patient (or proxy) interview and medical record review, with antithrombotic use (defined as any agent that inhibits thrombus formation by prolongation of the clotting time or primary antiplatelet effect) at stroke onset, coded as follows: (1) none, (2) antiplatelet agent only (aspirin and/or dipyridamole and/or clopidogrel), (3) warfarin with an INR of 2 to 3, or (4) warfarin with an INR of <2 or >3. The INR at presentation was documented for patients taking warfarin.

Follow-up mRS assessment was performed in real time at 28 and 90 days and at 1 and 2 years by in-person or telephone interview by a rater unaware of prestroke medication status, supplemented by medical record review, and physician assessment of patients with suspected recurrent events. Ethics committee approval was obtained from all participating institutions, and informed consent was obtained.

The consensus definition of AF (known or new diagnosis) was consistent with current European Society of Cardiology guidelines: “the presence on surface ECG of irregular RR intervals with the absence of consistent P waves, where atrial cycle length is variable and 200 ms.” Paroxysmal AF was defined as recurrent episodes self-terminating within 7 days. The World Health Organization definition of stroke was used.

Prespecified inclusion criteria were as follows: (1) new ischemic stroke within the ascertainment period (confirmed by brain imaging and/or autopsy), (2) new hemorrhagic stroke (intracerebral or subarachnoid hemorrhage), and (3) AF (known or new). We excluded patients with transient ischemic attack and those for whom prestroke medication data were unavailable.

Statistical Analyses

Comparisons of categorical variables were performed with χ² and Fisher tests. The Kruskal-Wallis test was used for nonparametric multigroup comparisons. Life-table analysis was performed for actuarial assessment of survival, stratified by prestroke antithrombotic therapy, with comparison of survival rates by the log-rank test to account for censoring. For regression analyses, the proportional-hazards assumption was not met, indicating that Cox regression techniques were invalid. Therefore, univariate and multivariable logistic regression was performed to determine the likelihood of survival at each time interval, with odds ratios (ORs) >1 indicating a greater likelihood of death. Multivariable logistic regression was also performed for analysis of good functional outcome (mRS = 0 to 2). The reference groups for therapeutic INR and subtherapeutic INR variables were all other prestroke antithrombotic categories. Analyses were performed with Stata (version 9). All significance tests were 2 sided.

Results

Clinical Characteristics

In the ascertainment year, 568 patients with new stroke were identified, 31.2% (177 of 568) of whom had AF. Two were excluded owing to unavailability of their prestroke medication. Of the remaining 175 patients, 3 had subarachnoid hemorrhage, 13 had primary intracerebral hemorrhage, and 159 had confirmed ischemic stroke on brain imaging or autopsy (2.8%, 5 of 175, were not imaged). Of the 16 with hemorrhagic stroke, 50% (8 of 16) were taking warfarin at stroke onset (3 with an INR >3). Among patients with ischemic stroke, a preexisting diagnosis of AF was present in 56.0% (89 of 159), and AF was detected at or shortly after stroke onset in the remainder. Paroxysmal AF was identified in 31.4% (50 of 159). Antiplatelet therapy was prescribed before stroke onset in 44.0% (70 of 159), warfarin in 17.0% (27 of 159), and no antithrombotic therapy in 39.0% (62 of 159). Almost one third (30.3%, 27 of 89) of patients with known AF were on warfarin therapy at stroke onset; 48% (13 of 27) had an INR <2.0, and 52% (14 of 27) had an INR ≥2.0.

Clinical characteristics are presented in Table 1, stratified by antithrombotic therapy. Significant between-group differences were observed for previous stroke, diabetes mellitus, hyperlipidemia, and coronary artery disease. Patients with an INR <2 were less likely to have completed second-level (high school) education compared with those with an INR of 2 to 3 (9.1% versus 54.6%, P = 0.03). No other socioeconomic differences were detected for university attendance, employment, and health insurance status.

No difference in prestroke disability, poststroke disability (mRS), or acute NIHSS score was observed. Hemorrhagic transformation of the infarct was detected on brain imaging in 2.5% (4 of 159), none of whom were taking warfarin.
Late Survival: Ischemic Stroke
Complete follow-up was available for 97.5% (155 of 159) of ischemic stroke patients. At 2 years, the probability of survival in patients with an INR of 2 to 3 at stroke onset was 92.3%, compared with 15.4% in those with an INR <2, 47.1% with antiplatelet therapy, and 55.3% in those on no antithrombotic therapy (log-rank \( P = 0.003 \); Figure 1 and online-only Table I).

An INR of 2 to 3 at stroke onset was associated with significant survival benefit at 2 years, with an OR for death of 0.07 (95% CI, 0.01 to 0.59; \( P = 0.01 \)). Conversely, a subtherapeutic INR at onset was associated with an increased likelihood of death at 2 years (OR = 6.5; 95% CI, 1.4 to 30.5, \( P = 0.02 \)). Increasing age (OR = 1.1 per 1-year increase; 95% CI, 1.05 to 1.1; \( P < 0.001 \)), higher NIHSS score (OR = 1.2 per 1-point increase; 95% CI, 1.1 to 1.2; \( P < 0.001 \)), and greater prestroke mRS score (OR = 1.4; 95% CI, 1.1 to 1.7; \( P = 0.009 \)) were also associated with a greater likelihood of death at 2 years. Similar findings were observed for fatality at the 1-year follow-up.

In a multivariable regression model including therapeutic INR, subtherapeutic INR, age, NIHSS score, and prestroke mRS score, therapeutic INR at stroke onset was independently associated with a survival benefit at 2 years (adjusted OR for death = 0.08; 95% CI, 0.01 to 0.78; \( P = 0.03 \)). Subtherapeutic INR remained an independent predictor of 2-year fatality (adjusted OR = 12.6; 95% CI, 2.0 to 80.1; \( P = 0.007 \)). Similar findings were observed at 1 year.

When the analysis was repeated after exclusion of early deaths (<28 days), the findings were unchanged (adjusted OR with therapeutic INR at 2 years = 0.1, \( P = 0.04 \)). However, when the 28-day mRS score was included in the models instead of NIHSS score as a measure of stroke severity, the 2-year survival benefit of therapeutic INR was attenuated (adjusted OR = 0.2, \( P = 0.09 \); online-only Table II).

Correlation Between INR and mRS Score
The INR at ischemic stroke onset was inversely correlated with mRS at early and late time intervals after stroke (90-day \( \rho = -0.44, P = 0.003 \)). The observed correlation was high at all follow-up assessments (2-year \( \rho = -0.65, P = 0.0003 \); Table 2).

Table 1. Clinical Characteristics of Patients With Ischemic Stroke and AF (n = 159)

<table>
<thead>
<tr>
<th></th>
<th>No Antithrombotic Agent (n = 62)</th>
<th>Antiplatelet Agent (n = 70)</th>
<th>Warfarin (n = 13)</th>
<th>Warfarin (n = 14)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR), y</td>
<td>77 (66–83)</td>
<td>82 (72–86)</td>
<td>76 (69–80)</td>
<td>77 (70–80)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean INR</td>
<td>...</td>
<td>...</td>
<td>1.4</td>
<td>2.5</td>
<td>...</td>
</tr>
<tr>
<td>Sex, n (% female)</td>
<td>31 (50%)</td>
<td>38 (54.3%)</td>
<td>6 (46%)</td>
<td>9 (64.3%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Prior stroke, n (%)</td>
<td>4 (6.5%)</td>
<td>21 (30%)</td>
<td>3 (23.1%)</td>
<td>7 (50%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>32 (53%)</td>
<td>47 (70%)</td>
<td>5 (38.5%)</td>
<td>10 (71.4%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)*</td>
<td>2 (3.3%)</td>
<td>7 (10%)</td>
<td>3 (23.1%)</td>
<td>3 (21.4%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)*</td>
<td>12 (20%)</td>
<td>27 (39%)</td>
<td>8 (61.5%)</td>
<td>5 (35.7%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>18 (29.5%)</td>
<td>38 (54.3%)</td>
<td>6 (46.2%)</td>
<td>10 (71.4%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>33 (57.9%)</td>
<td>41 (60%)</td>
<td>8 (61.5%)</td>
<td>6 (42.9%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Prior TIA, n (%)</td>
<td>9 (15%)</td>
<td>17 (24.3%)</td>
<td>3 (23.1%)</td>
<td>2 (14.3%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Paroxysmal AF, n (%)</td>
<td>22 (35.5%)</td>
<td>22 (31.4%)</td>
<td>0</td>
<td>4 (2.9%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Median prestroke mRS score (IQR)</td>
<td>0 (0–0)</td>
<td>0 (0–2)</td>
<td>0.5 (0–3)</td>
<td>2 (–4)</td>
<td>0.2</td>
</tr>
<tr>
<td>Median mRS score &lt;72 h (IQR)</td>
<td>4 (2–5)</td>
<td>4 (3–5)</td>
<td>5 (3–5)</td>
<td>4 (3–4)</td>
<td>0.3</td>
</tr>
<tr>
<td>Median NIHSS score &lt;72 h (IQR)†</td>
<td>6.5 (2–14)</td>
<td>5.5 (3.5–13)</td>
<td>6.5 (4.5–12)</td>
<td>4 (2–8)</td>
<td>0.6</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>8 (14.3%)</td>
<td>30 (43.5%)</td>
<td>4 (30.8%)</td>
<td>6 (42.9%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>26 (45.6%)</td>
<td>56 (81.2%)</td>
<td>10 (76.9%)</td>
<td>12 (85.7%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; INR, International Normalized Ratio; IQR, interquartile range; TIA, transient ischemic attack; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

*1.4–9.7% data missing.
†n = 146.

Figure 1. Kaplan–Meier curve of 2-year survival, stratified by antithrombotic medication category at ischemic stroke onset. INR indicates International Normalized Ratio.
Late Disability: Ischemic Stroke

Improved functional status was associated with therapeutic INR at early and late time intervals after stroke onset (Figure 2). Therapeutic INR was associated with improved functional outcome (mRS=0 to 2) at 1 year (OR=3.2; 95% CI, 1.0 to 10.0; P=0.05). On logistic regression, after adjusting for age, prestroke mRS, and low INR, this association remained (OR=4.8; 95% CI, 1.45 to 23.8; P=0.04). When NIHSS was included in the model, the association between therapeutic INR and good outcome was no longer significant (OR=2.24; P=0.35), suggesting that it was partially mediated by stroke severity.

At 2 years, the association between therapeutic INR and good functional outcome was no longer observed, most likely related to a deterioration in functional status of some patients in the INR 2 to 3 group between 1 and 2 years. On multivariable analysis, increasing age (OR=0.9; 95% CI, 0.85 to 0.93; P<0.001), higher NIHSS score (OR=0.8; 95% CI, 0.76 to 0.92; P<0.001), greater prestroke mRS score (OR=0.4; 95% CI, 0.2 to 0.7; P=0.002), and subtherapeutic INR (OR=0.08; 95% CI, 0.01 to 1.04; P=0.05) predicted a lower likelihood of good functional outcome at 2 years.

Early Recovery After Ischemic Stroke

To examine the relation between therapeutic INR at stroke onset and early improvement on the mRS, we performed a post hoc analysis of mRS change (between 72 hours and 28 days) stratified by prestroke antithrombotic status. For this analysis, patients were classified as “not improved or deteriorated” (mRS change=0 or positive) and “improved” (mRS change negative). Improved mRS score at 28 days occurred in 64.3% of patients with an INR of 2 to 3 compared with 34.5% without therapeutic INR at stroke onset (P=0.04; Figure 2). On exploratory 2-group analysis, some evidence was apparent of improved early recovery with an INR of 2 to 3 compared with antiplatelet (P=0.04) and subtherapeutic INR (P=0.054) groups, but these were not significant after correction for multiple comparisons (Bonferroni corrected P=0.017).

Late Survival and Disability, Including Hemorrhagic Stroke

For ischemic and hemorrhagic stroke patients combined, 2-year survival for those with an onset INR of 2 to 3 was 70.5% compared with 14.3% in those with a nontherapeutic INR (INR <2 or >3; log-rank P<0.001). An INR of 2 to 3 remained associated with survival benefit at 2 years, after inclusion of patients with hemorrhagic stroke (OR=0.27; 95% CI, 0.09 to 0.88; P=0.03). After adjusting for age, NIHSS score, prestroke mRS score, and INR category, a trend was observed for the association of therapeutic INR with survival benefit at 2 years (OR for death=0.24; 95% CI, 0.05 to 1.12; P=0.07).

INR at stroke onset remained inversely correlated with 2-year mRS score (Spearman ρ=−0.36, P=0.04) for ischemic and hemorrhagic stroke combined. However, when functional outcome was dichotomized as good (mRS=0 to 2) or poor (mRS=3 to 6), no association between an INR of 2 to 3 at onset and good outcome at 1 and 2 years was observed after inclusion of patients with hemorrhagic stroke.

Discussion

The main finding of our study is that therapeutic warfarin anticoagulation at stroke onset was associated with a substantial improvement in late survival, with an estimated 92% of adequately anticoagulated patients alive at 2 years compared with 15% to 55% in other treatment groups. The benefit remained after adjusting for other known predictors of poor stroke outcome, including age, NIHSS score, and prestroke functional status. After exclusion of deaths within the first 28 days of stroke onset, therapeutic INR remained associated with improved survival, indicating ongoing benefit at later time points. Although attenuated, late benefit persisted after inclusion of data from patients with hemorrhagic stroke, which has been unavailable to date. This provides evidence of the net influence of therapeutic anticoagulation on stroke outcome for all stroke types, which is most relevant when advising individual patients who are considering warfarin therapy.

These findings were supported by a similar benefit for early and late functional outcome. We observed an inverse correlation between INR at stroke onset and mRS score at all early and late time intervals, which was most apparent at 2 years. Although therapeutic INR was not associated with a clear reduction in initial stroke severity, serial mRS measures revealed that the improvement in disability associated with
adequate anticoagulation began in the first week, was maximal by 28 days, and persisted at 1 year. However, between 1 and 2 years, a third phase of functional status was observed in the INR 2 to 3 group, with late deterioration in some patients, so that the benefit associated with therapeutic INR diminished. This may reflect late recurrent stroke (in 1 patient), late functional deterioration after initial rehabilitation gains, and/or unmeasured comorbid illness.

Several possible explanations exist for the benefits observed in our study. In a detailed magnetic resonance imaging study, an INR of 2 to 3 was associated with smaller acute diffusion- and perfusion-weighted imaging lesion volumes, lower final infarct volumes, greater frequency of small distal infarcts, and lower acute NIHSS scores. Possible mechanisms include smaller embolus size, enhanced early spontaneous fibrinolysis, and reduced thrombus propagation. In the Canadian Stroke Network Registry, an INR of 2 to 3 was associated with milder stroke at onset. In that study, the benefit of therapeutic warfarin on early disability and death was eliminated after adjusting for stroke severity, suggesting that the effect was partly mediated by less severe stroke. We and others observed no relation between prestroke antithrombotic therapy and initial stroke severity. Although the late survival benefit with therapeutic INR remained after adjusting for NIHSS score in our study, when 28-day mRS score was used as an alternative measure of stroke severity, the benefit was attenuated (online-only Table III). The association between therapeutic INR and late functional outcome was also attenuated after adjusting for NIHSS score, supporting the interpretation that stroke severity may partially account for the relation.

We also found that subtherapeutic INR was independently associated with greater late mortality compared with no antithrombotic or antiplatelet therapy. We had anticipated that poor INR control would be associated with outcomes similar to those of nonwarfarin treatment strategies, as reported in earlier hospital studies. Poor anticoagulation control is associated with higher rates of stroke, coronary events, and death compared with good control or no warfarin therapy. However, despite persisting after adjustment for other important predictors of outcome, it may also be explained by residual confounding by other unidentified prognostic factors.

Despite evidence from randomized trials, fewer than one third of patients with known AF were prescribed warfarin, and almost 40% were not prescribed any antithrombotic agent before stroke onset. Similar rates have been reported internationally. Of patients prescribed warfarin, only half were in the recommended INR range. Although patients had similar age profiles, comorbid illnesses, and anticoagulation monitoring, those with nontherapeutic INR were less likely to have completed second-level (high school) education, possibly indicating poorer compliance or health literacy in this group.

Some hospital-based studies have described improved disability at hospital discharge or reduced 1-month mortality associated with therapeutic anticoagulation. Strengths of our study include its population-based design, with the use of validated ascertainment methods of all hospital- and community-treated patients with AF-associated stroke. This minimizes bias and increases the generalizability of our findings. Our prospective study design allowed collection of potential confounder variables and serial mRS measures to describe the early trajectory of poststroke recovery stratified by antithrombotic treatment. The high follow-up rates allowed accurate description of important late-outcome measures. Inclusion of hemorrhagic stroke enabled analysis of the net influence of therapeutic INR on outcome for all stroke types, which will better inform decision making for individual patients.

We acknowledge some limitations. The small group size of warfarin-treated patients resulted in wide CIs for ORs and other effect measures. Although the findings have internal validity in this population-based cohort, further research is needed in larger samples to determine the external validity of our findings. Late outcomes included death, and we acknowledge a limitation that changes in disability levels may not precisely reflect the functional outcome of survivors. Cause of death was not ascertained; therefore, we cannot exclude the possibility of nonvascular causes of death (for example, cancer) that contributed to our results. We cannot exclude the possibility that improved outcomes in patients with therapeutic INR may be partly related to unmeasured factors associated with improved INR control, which may influence stroke outcome (for example, cognition, other comorbidities, or medication compliance). However, patients in the INR 2 to 3 group were similar to the comparison groups for some important prognostic factors, such as age and prestroke function, and benefit was observed, despite greater frequency of past stroke and diabetes mellitus, both associated with poor outcomes in previous studies.

Increasing anticoagulation prophylaxis may prevent a substantial proportion of AF-associated stroke at the population level. Our data indicate that therapeutic INR at stroke onset is associated with more rapid early improvement and greater late survival after stroke in unselected patients. As yet, it is unclear whether newer agents such as dabigatran and rivaroxaban will provide similar benefits for stroke outcome, despite their proven benefits for stroke prevention and reduction in major hemorrhage rates. Future research should investigate approaches to improve the identification and selection of appropriate patients with AF for anticoagulation therapy and to optimize delivery in clinical practice.

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Disclosures

None.
References

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SUPPLEMENTAL MATERIAL

Improved late survival and disability after stroke with therapeutic anticoagulation for atrial fibrillation. A population study.

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Supplemental Methods

• **Ascertainment methods:**

  Ascertainment included “hot” and “cold” pursuit using multiple overlapping hospital and community sources, according to recommended criteria for rigorous epidemiological studies\(^1\). Ascertainment sources in the community included North Dublin General Practitioners and nursing homes (95% participation). A 5-day minor stroke/TIA clinic was established to encourage community referral of eligible patients. Hospital ascertainment sources included regular review of referrals to outpatient clinics, daily reviews of emergency department attendees, hospital admissions and consultation requests for Neurology, Geriatric Medicine, Ophthalmology, and Vascular Surgery services, and bi-weekly review of referrals for brain and vascular imaging. Ascertainment was conducted in all nine North Dublin hospitals (three acute general and six non-acute specialist), supplemented by review of pathology department records, death certificates, and coroner records. Cause of death was not ascertained in those patients who died during the follow-up period.
## Supplemental Tables & Results

Web-Table S1. Life-table analysis of survival stratified by antithrombotic use at ischaemic stroke onset

<table>
<thead>
<tr>
<th>Time</th>
<th>Warfarin (INR 2-3)</th>
<th></th>
<th>Warfarin (INR&lt;2)</th>
<th></th>
<th>Antiplatelet</th>
<th></th>
<th>No anti-thrombotic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survival</td>
<td>95% CI</td>
<td>Survival</td>
<td>95% CI</td>
<td>Survival</td>
<td>95% CI</td>
<td>Survival</td>
<td>95% CI</td>
</tr>
<tr>
<td>7 days</td>
<td>100%</td>
<td>-</td>
<td>92.3%</td>
<td>56.6-98.9</td>
<td>90.0%</td>
<td>80.2-95.1</td>
<td>95.2%</td>
<td>85.7-98.4</td>
</tr>
<tr>
<td>28 days</td>
<td>100%</td>
<td>-</td>
<td>92.3%</td>
<td>56.6-98.9</td>
<td>82.3%</td>
<td>71.8-89.9</td>
<td>82.3%</td>
<td>70.3-89.8</td>
</tr>
<tr>
<td>90 days</td>
<td>100%</td>
<td>-</td>
<td>61.5%</td>
<td>30.8-81.8</td>
<td>75.7%</td>
<td>63.9-84.1</td>
<td>75.8%</td>
<td>63.1-84.6</td>
</tr>
<tr>
<td>1 year</td>
<td>92.3%</td>
<td>56.6-98.9</td>
<td>38.5%</td>
<td>14.1-62.8</td>
<td>57.1%</td>
<td>44.8-67.7</td>
<td>65.6%</td>
<td>52.3-76.1</td>
</tr>
<tr>
<td>2 years</td>
<td>92.3%</td>
<td>56.6-98.9</td>
<td>15.4%</td>
<td>2.5-38.8</td>
<td>47.1%</td>
<td>35.1-58.2</td>
<td>55.3%</td>
<td>41.9-66.8</td>
</tr>
</tbody>
</table>
• **Web-Table S2. 2-year survival – ischaemic stroke**

To determine the association of therapeutic INR on survival beyond 28 days, the log-rank test for equality of survivor function, univariate and multivariable logistic regression analyses were performed in all patients alive at 28 days (n=135). The log-rank test was significant (p=0.0001). Therapeutic INR was associated with improved late survival in these analyses.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate logistic regression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic INR (univariate logistic regression for 2 year fatality)*</td>
<td>0.11</td>
<td>0.01-0.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Subtherapeutic INR (univariate logistic regression for 2 year fatality)</td>
<td>9.2</td>
<td>1.9-43.8</td>
<td>0.005</td>
</tr>
</tbody>
</table>

| Multivariable logistic regression (model including therapeutic INR, subtherapeutic INR, age, premorbid mRS and 72-hour NIHSS) |            |            |    |
| Therapeutic INR | 0.1 | 0.01-0.94 | 0.048 |
| Subtherapeutic INR | 12.6 | 2.0-77.9 | 0.006 |

• **Web-table S3. 2-year survival after ischaemic stroke, adjusting for stroke severity defined as 28-day mRS (n=135)**

In an exploratory analysis, we determined whether the relationship between therapeutic INR and 2-year survival might be partially mediated by stroke severity, as defined by 28-day mRS instead of 72-hour NIHSS. The adjusted OR for survival benefit associated with therapeutic INR was attenuated, suggesting that the benefit was partly mediated via reduced stroke severity in this group.

| Multivariable logistic regression (model including therapeutic INR, subtherapeutic INR, age, premorbid mRS and 28-day mRS) |            |            |    |
| Therapeutic INR | 0.2 | 0.02-1.4 | 0.09 |
| Subtherapeutic INR | 18.1 | 2.3-153.4 | 0.01 |

• **Hospitalization:**

6 (3.4%) of the AF-associated strokes were not hospitalized. This high hospitalization rate reflects the severe and disabling profile of AF-stroke.
• **Proportions lost to follow-up for Rankin assessments:**

<table>
<thead>
<tr>
<th>mRS missing at time-point</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>90-day</td>
<td>4</td>
<td>2.3%</td>
</tr>
<tr>
<td>1-year</td>
<td>6</td>
<td>3.4%</td>
</tr>
<tr>
<td>2-year</td>
<td>5</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

• **Post-stroke medication analysis**

As part of the North Dublin stroke study, information on medication post-stroke was recorded post-stroke (within 72 hours) and again at hospital discharge in hospitalized patients.

In summary:

<table>
<thead>
<tr>
<th>Pre-stroke Antithrombotic category</th>
<th>Patients on warfarin post-stroke at discharge or death</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antithrombotic (n=62)</td>
<td></td>
<td>19</td>
<td>31%</td>
</tr>
<tr>
<td>Antiplatelet only (n=70)</td>
<td></td>
<td>12</td>
<td>17%</td>
</tr>
<tr>
<td>Warfarin (n=27)</td>
<td></td>
<td>19</td>
<td>70%</td>
</tr>
</tbody>
</table>

**Supplemental References**

1. Feigin VL, Carter K. Stroke incidence studies one step closer to the elusive gold standard? Stroke 2004;35;2045-2047
心房細動に対する抗凝固療法による脳卒中後の遠隔期生存率および障害の改善 — 一般住民を対象とした研究

Improved Late Survival and Disability After Stroke With Therapeutic Anticoagulation for Atrial Fibrillation — A Population Study

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Stroke 2011; 42: 2503-2508