Are Cost Benefits of Anticoagulation for Stroke Prevention in Atrial Fibrillation Underestimated?

Paul S.J. Miller, MSc; Fredrik L. Andersson, PhD; Lalit Kalra, PhD

Background and Purpose—Stroke outcomes in patients with atrial fibrillation (AF) tend to be worse than those in patients without AF. The objective of this study was to evaluate whether the cost benefits of anticoagulation for stroke prevention in AF may currently be underestimated by existing economic models that do not distinguish between different stroke outcomes.

Methods—A literature review was conducted in 3 areas: (1) studies comparing stroke outcomes in AF and non-AF patients; (2) studies providing long-term cost of stroke estimates; and (3) studies modeling the cost-effectiveness of anticoagulation with a vitamin K antagonist (eg, warfarin) in AF patients.

Results—There is considerable evidence that stroke in AF patients has a worse outcome than in patients without AF, including higher mortality, severity, and recurrence rates, and greater functional impairment and dependency. Estimates of the long-term cost of stroke of different severities were between US $24,991 for a mild stroke over 5 years and US $142,251 for a major ischemic stroke over a lifetime (2004 prices). The cost of a severe ischemic stroke may typically be 3-times that of mild stroke. However, cost-effectiveness models for anticoagulation in patients with AF have used average (not AF-specific) cost-of-stroke data, and most have used stroke severity distributions derived from clinical trials, which may differ from those in clinical practice.

Conclusions—Existing economic models underestimate the cost benefits of anticoagulation for stroke prevention because they do not adjust for poorer outcomes associated with cardioembolic strokes. (Stroke. 2005;36:360-366.)

Key Words: anticoagulants ■ arrhythmia ■ cost-benefit analysis ■ primary prevention ■ stroke

Recent years have seen an increasing emphasis on the use of health economic data, in conjunction with evidence of clinical effectiveness, for the development of clinical guidelines.1,2 This is particularly important for stroke, a disease characterized by a high prevalence, as well as a high burden of illness and economic cost, but in which preventive strategies such as blood pressure control, smoking cessation, diet and exercise have been shown to be effective. Of the preventive measures for stroke in patients with atrial fibrillation (AF), anticoagulation has been associated with the greatest benefits, resulting in a 67% to 80% reduction in the risk of stroke.3 Atrial fibrillation affects 5% of all elderly people and increases the risk of stroke 5-fold compared with patients in normal sinus rhythm.4,5 Because both the incidence of AF and the stroke risk attributable to AF increase with age (the latter being 1.5% at age 50 to 59 years; 9.9% at 70 to 79 years; and 23.5% at 80 to 89 years), AF and stroke will pose major societal costs over the coming decades.4,6-9 Cost-effectiveness models of anticoagulation for the prevention of stroke in patients with AF are based on the incremental change in costs and outcomes (eg, quality-adjusted life years) associated with anticoagulant therapy, treatment-related bleeding events, and ischemic strokes. The objective of this review was to evaluate whether the cost benefits of anticoagulation for stroke prevention in AF may currently be underestimated by existing economic models that do not account for the different outcomes of cardioembolic stroke in people with AF compared with strokes in patients without AF. A literature review was conducted in 3 areas: (1) studies comparing stroke outcomes in patients with and without AF; (2) studies providing long-term cost-of-stroke estimates; and (3) studies modeling the cost-effectiveness of anticoagulation.

Materials and Methods

We conducted a literature review of studies comparing stroke outcomes in patients with and without AF, studies estimating the cost of stroke, and studies modeling the cost-effectiveness of anticoagulation. Searches were conducted on MEDLINE in December 2003, including results from 1966 up to that date, with the following search criteria: “stroke outcome/severity/cost” AND “atrial fibrillation;” “cost/cost-effectiveness/economic evaluation” AND “anticoagulation” AND “atrial fibrillation.” The initial search identified 114
articles. Studies reporting primary data analysis, economic models, or cost-of-stroke data with at least 1 year of follow-up were selected for inclusion. The final analysis included 14 studies comparing stroke outcomes in AF and non-AF patients, 15 cost-of-stroke studies, and 9 cost-effectiveness modeling studies.

Results

Stroke Outcomes in AF

Earlier studies of stroke outcomes focused on mortality and stroke recurrence rates, whereas later studies have considered stroke severity in addition to functional and neurological impairment among stroke survivors. Collectively, studies analyzing ≈10 000 strokes clearly demonstrate that stroke in patients with AF has worse outcomes than strokes in patients in sinus rhythm (non-AF stroke) (Table 1).

Overall, ischemic stroke associated with AF is approximately twice as likely to be fatal as non-AF stroke. Adjusting for age and comorbidities, short-term mortality rates from stroke (in-hospital or 1 month after stroke) were significantly increased in the presence of AF (10.12–17.19–23 (19% to 35%) compared with no AF (5% to 14%; Table 1).10.12–14.16.19 Atrial fibrillation also independently predicted higher 3-month stroke mortality after controlling for age, gender, and other baseline variables,10 higher mortality 1 year after stroke in multivariate analyses,18.19.22 and higher relative risk of death at 6 months.13

At 6 months11 and 1 year19.22 after an initial stroke, recurrence rates are ≳2-times higher in patients with AF compared with those without AF (Table 1). Various studies have demonstrated more severe (larger) brain lesions,12.17.20 a greater incidence of abnormal computed tomograms,13 and more patients with cortical involvement (68% versus 43%)20 or an anterior circulation infarct (34% versus 25%)10 among stroke patients with AF. Stroke was more likely to be severe (evaluated on the basis of neurological impairment during the initial hospitalization) or fatal in subjects with AF,19 and it contributed to masking any differences between AF stroke and non-AF stroke patients.

Stroke in patients with AF is associated with more impairment measured by the modified Rankin Scale at 30 days,10 3 months,10 and 1 year,22 as well as with greater dependency measured on the Barthel Index in the acute phase,19 at 3 months,10.19 and at 6 months (Table 1).19 For example, 33% of non-AF patients had acute severe dependency, and this decreased to 16% at 3 and 6 months, whereas among AF patients 73% had severe dependency in the acute phase, 58% at 3 months, and 36% at 6 months.19 Two studies10.20 have shown that a significantly lower proportion of AF stroke patients are discharged to their own home (Table 1), although these analyses did not adjust for age. In addition, 30% more patients with than without AF were institutionalized (9% versus 6%, respectively).10

Cost of Stroke

Long-term cost estimates show that the cost of stroke is substantial in all countries.24–40 Lifetime estimates of the cost of a stroke per patient range between US $25 558 (all stroke types) and US $142 251 (major ischemic stroke) after adjustment to dollars and 2004 prices (base costs, Swedish krona 180 000 in 199126 and £75 985 in 1996,24 respectively). Three publications reported costs for strokes of different severities (Table 2).26.34.35 The cost increments were between 1.5- and 3-fold. The lowest cost was for all mild strokes over 5 years (US $24 991)35 and the highest was for a major ischemic stroke over a lifetime (US $142 251, as noted).34 Importantly, no publications were found reporting costs of stroke specifically for a population with AF. It has been shown that hospitalized AF patients incur higher costs than matched patients without AF,41 although interventions for the arrhythmia, such as cardioversion, would have contributed to the cost differential in this analysis.

Economics of Anticoagulation

The cost-effectiveness of anticoagulation among AF patients classified as high-risk of stroke is clearly established, whereas cost-effectiveness estimates among patients at lower risk may be more sensitive to the input assumptions of economic models. The findings of the economic models shown in Table 3 represent the current body of cost-effectiveness evidence.33,42–48 The results of all of these studies show that in medium- to high-risk patients with AF or older patients with AF, whether male or female, anticoagulation is dominant (increases quality-adjusted life-years and is cost-saving) or has a low marginal cost-effectiveness ratio (a low additional cost per quality-adjusted life-year gained) in comparison with no anticoagulant therapy33,42,46–48 and in comparison with aspirin,44.45 whereas low-risk AF populations are associated with a higher marginal cost-effectiveness ratio.45

The cost of AF strokes in these models will be characterized by the severity distribution used and the average “unit” costs attached to each stroke severity category. Table 4 shows the distributions of stroke event severity that were used in 5 published economic models. Four use the severity distribution observed in randomized controlled trials of anticoagulation in AF patients rather than from unselected patients in routine clinical practice.33,44,45,47 One of these is based on a single, small study (n=420) in which only 15 strokes occurred. Thomson et al46 state that no valid published studies reported the risk of different outcomes after stroke associated with AF. Only Thomson et al use epidemiological data for severity—based on a personal communication with the Oxfordshire Community Stroke Project. Perhaps as expected, the proportion of fatal strokes in this study using epidemi-
TABLE 1. Studies Comparing Outcomes in AF Stroke and Non-AF Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size (AF vs non-AF Strokes)</th>
<th>Study Duration</th>
<th>Outcome Measure</th>
<th>Results (AF vs non-AF Strokes)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolf et al Framingham study (1983)11</td>
<td>59 vs 442</td>
<td>30-day study, 6-month follow-up</td>
<td>Mortality at 30 d: Stroke recurrence at 6 mo:</td>
<td>17% vs 19%, not significant 47% vs 20%, P=0.05</td>
</tr>
<tr>
<td>Britton and Gustafsson (1985)12</td>
<td>92 vs 196</td>
<td>Acute phase</td>
<td>Mortality in-hospital:</td>
<td>26% vs 5%, P&lt;0.05</td>
</tr>
<tr>
<td>Candelise et al (1991)13</td>
<td>211 vs 837</td>
<td>1-mo study, 6-mo follow-up</td>
<td>Mortality at 1 mo: Mortality at 6 mo:</td>
<td>27% vs 14%, P&lt;0.05; RR (adjusted for other factors) = 1.55 40% vs 20%, P&lt;0.05; RR (adjusted for other factors) = 1.74</td>
</tr>
<tr>
<td>Gustafsson and Britton (1991)14</td>
<td>88 vs 188</td>
<td>5 y</td>
<td>Mortality at 1 mo: Mortality at 6 mo:</td>
<td>35% vs 7%, P&lt;0.05 40% vs 20%, P&lt;0.05</td>
</tr>
<tr>
<td>Broderick et al (1992)15</td>
<td>318 (total)</td>
<td>30 d</td>
<td>Mortality at 30 d:</td>
<td>AF an independent predictor, P=0.05</td>
</tr>
<tr>
<td>Sandercock et al (1992)16</td>
<td>115 vs 560</td>
<td>30-d study, up to 6.5-y follow-up</td>
<td>Mortality at 30 d:</td>
<td>AF associated (multivariate model), P=0.005</td>
</tr>
<tr>
<td>Censori et al (1993)17</td>
<td>172 (total)</td>
<td>6 mo</td>
<td>Mortality at 30 d: Handicap (modified Rankin Scale) at 30 d:</td>
<td>AF associated (multivariate model), P=0.005 23% vs 8%, P&lt;0.05</td>
</tr>
<tr>
<td>Anderson et al (1994)18</td>
<td>321 (total)</td>
<td>1-year follow-up</td>
<td>Mortality at 30 d:</td>
<td>AF associated (multivariate model), P=0.05</td>
</tr>
<tr>
<td>Lin et al Framingham study (1996)19</td>
<td>103 vs 398</td>
<td>30-d study, 1-y follow-up in subsample</td>
<td>Mortality at 30 d: Stroke recurrence at 1 y (subsample): Stroke severity:</td>
<td>Severe or fatal in 39% vs 28%, P=0.048</td>
</tr>
<tr>
<td>Jørgensen et al Copenhagen stroke study (1996)20</td>
<td>217 vs 968</td>
<td>From acute admission to end of rehabilitation</td>
<td>Mortality in-hospital: Functional outcome at discharge: Neurological outcome at discharge: Length of hospital stay: Discharge to own home:</td>
<td>OR=1.7 (multiple regression), P=0.005 Barthel Index 66.8 vs 78.0, P=0.0007 Scandinavian neurological stroke scale 46.3 vs 49.8, P=0.003 No. of days 50.4 vs 39.8, P=0.001 48% vs 69%, P=0.00001 61.4% vs 71.4%, P=0.00001</td>
</tr>
<tr>
<td>Lamassa et al European BIOMED study (2001)21</td>
<td>803 vs 3659</td>
<td>3 mo</td>
<td>Mortality at 30 d: Dependency at 3 mo (subsample): Impairment at 3 mo (subsample): Length of hospital stay: Discharge to own home:</td>
<td>19.1% vs 12.0%, P&lt;0.001 32.8% vs 19.9%, P&lt;0.001 61.4% vs 71.4%, P&lt;0.001 60.8 vs 54.9, P&lt;0.001 74% vs 84%, P&lt;0.001</td>
</tr>
<tr>
<td>Appelros et al (2002)22</td>
<td>90 vs 287</td>
<td>28 d</td>
<td>Mortality at 28 d: Stroke severity: Stroke recurrence at 1 y:</td>
<td>OR=2.43 (multivariate model), P&lt;0.01 OR=2.1 (univariate model), 95% CI 1.0–4.8 OR=1.6 (univariate model), 95% CI 0.8–3.1, not significant</td>
</tr>
<tr>
<td>Appelros et al (2003)23</td>
<td>90 vs 287</td>
<td>1-y follow-up</td>
<td>Mortality at 1 y: Stroke recurrence at 1 y:</td>
<td>HR=2.4 (multivariate model), 95% CI 1.6–3.6 OR=2.1 (univariate model), 95% CI 1.0–4.8</td>
</tr>
<tr>
<td>Dulli et al (2003)24</td>
<td>216 vs 845</td>
<td>Acute phase</td>
<td>Bedridden state after stroke:</td>
<td>41.2% vs 23.7%, P&lt;0.0005; OR (multivariate model) 2.23, P&lt;0.0005</td>
</tr>
</tbody>
</table>

*Results presented as percentage of patients unless otherwise specified. CI indicates confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.
demonstrated in existing economic models, is likely to be effectiveness of anticoagulation therapy, which has been suggested that AF strokes have a higher cost compared with greater functional impairment and dependency. These factors ing higher mortality, severity, and recurrence rates and AF has worse outcomes than non-AF–related strokes, includ-

utilities (ie, quality-of-life estimates).

differential risk of events, health care, patient resource use events. These parameters are a function of factors such as the distribution of strokes. Estimates of the cost of long-term care and the proportion of patients requiring nursing home care used in cost-effectiveness models also vary. Again, these are not based on resource use evaluated from an AF population.

Discussion

Economic models to assess the cost-effectiveness of anticoagulation in AF for the primary prevention of ischemic stroke are based on 3 input parameter estimates, namely the change in patients with AF uses AF-specific stroke cost data. Instead, more generic stroke cost and price estimates are used. As with the long-term estimates illustrated in Table 2, the costs applied to stroke events vary with the sources of data, assumptions, and the extrapolated time periods used. The acute (one-time) cost of severe stroke has been considered to be 2.8-fold or 3.5-fold that of mild stroke. These costs are then weighted based on the assumed severity distribution of strokes. Estimates of the cost of long-term care and the proportion of patients requiring nursing home care used in cost-effectiveness models also vary. Again, these are not based on resource use evaluated from an AF population.

logical data are higher than in those using data from clinical trials (Table 4).

None of the 5 cost-effectiveness models for anticoagulation in patients with AF uses AF-specific stroke cost data. Instead, more generic stroke cost and price estimates are used. As with the long-term estimates illustrated in Table 2, the costs applied to stroke events vary with the sources of data, assumptions, and the extrapolated time periods used. The acute (one-time) cost of severe stroke has been considered to be 2.8-fold or 3.5-fold that of mild stroke. These costs are then weighted based on the assumed severity distribution of strokes. Estimates of the cost of long-term care and the proportion of patients requiring nursing home care used in cost-effectiveness models also vary. Again, these are not based on resource use evaluated from an AF population.

The monetary valuation placed on stroke events is a key component of the economic assessment of events that could be avoided by anticoagulation. Large variations arise because of the different ways that stroke services are organized and the different service needs of different subpopulations. In particular, the length of acute stay, type of acute care ward, the existence of hospital-based rehabilitation, and staff skills mix vary considerably and are key drivers of acute care costs. Variation in postacute care services is even greater. Impairment and dependency increase the need for health and social services and family support. Discharge from hospital to a residential or nursing home represents the largest share of total costs. However, rehabilitation services and institutional care are not formally provided in many health care systems; therefore, a great deal of the unpaid informal care is not included in the cost estimates. Variation in postacute care services is even greater. Impairment and dependency increase the need for health and social services and family support. Discharge from hospital to a residential or nursing home represents the largest share of total costs. However, rehabilitation services and institutional care are not formally provided in many health care systems; therefore, a great deal of the unpaid informal care is not included in the cost estimates. Variation in postacute care services is even greater. Impairment and dependency increase the need for health and social services and family support. Discharge from hospital to a residential or nursing home represents the largest share of total costs. However, rehabilitation services and institutional care are not formally provided in many health care systems; therefore, a great deal of the unpaid informal care is not included in the cost estimates. Variation in postacute care services is even greater.

The different service needs of different subpopulations are relevant to the potential underestimate of the average costs of stroke typical in AF patients compared with non-AF–related or total stroke events. Data sources for resource use and survival are important to the reliability of cost estimates. For resource use, studies rely on prospective data obtained from stroke registries, clinical or economic trials, and published or other expert opinion. For survival, longer-term epidemiological data are available, but there is a paucity of longer-term observational studies of stroke patients reporting cost data. Most economic studies of stroke follow-up patients for 1 or 2 years and use modeling techniques to extrapolate to lifetime costs (10 to 15 years for this population) based on mortality, progression through disability levels over time, and correlations between disability levels and cost. Generally, cost models based on studies with a longer time period of actual patient-specific resource use data will be more reliable.

### Table 2. Country-Specific Long-Term Cost of Stroke Estimates for Stroke of Different Severities

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>Cost Per Patient, as Publication Year Adjusted to 2004, US $*</th>
<th>Stroke Type and Time Period (lifetime estimate unless stated)</th>
<th>Extrapolation Methods: Actual Data—Projected Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Dewey et al (2003)</td>
<td>Aus $34 470 US $29 377</td>
<td>Lacunar infarction</td>
<td>A cost-of-illness model was used to estimate the total first-year costs and lifetime costs of stroke subtypes for all strokes (subarachnoid hemorrhages excluded) that occurred in Australia during 1997</td>
</tr>
<tr>
<td>UK</td>
<td>Youman et al (2003)</td>
<td>£15 306 US $24 991</td>
<td>All mild strokes, 5-y model</td>
<td>Resource use data from 12-mo randomized study (n=457); Markov model combines study data and literature, and projects cost to 5 y</td>
</tr>
<tr>
<td>UK</td>
<td>Caro et al (1999)</td>
<td>£27 995 US $48 956</td>
<td>Minor ischemic</td>
<td>3- to 12-mo resource use data from RCT and literature projected to 15 y; 3-mo to 7-y survival data from RCT and OCSP projected 7 to 15 y</td>
</tr>
<tr>
<td>UK</td>
<td>Miller et al (1999)</td>
<td>£75 985 US $142 251</td>
<td>Major ischemic</td>
<td>2002 All severe strokes, 5-y model</td>
</tr>
</tbody>
</table>

OCSP indicates Oxfordshire Community Stroke Project; RCT, randomized controlled trial.

*Local currency costs from the base year were adjusted to estimated 2004 costs, applying the US inflation rate (Consumer Price Index) for the appropriate period to all countries. Costs were then converted to US dollars using purchasing power parities (PPPs) for the most recent year available (2003). Costs are then weighted based on the assumed severity distribution of strokes. Estimates of the cost of long-term care and the proportion of patients requiring nursing home care used in cost-effectiveness models also vary. Again, these are not based on resource use evaluated from an AF population.

The different service needs of different subpopulations are relevant to the potential underestimate of the average costs of stroke typical in AF patients compared with non-AF–related or total stroke events. Data sources for resource use and survival are important to the reliability of cost estimates. For resource use, studies rely on prospective data obtained from stroke registries, clinical or economic trials, and published or other expert opinion. For survival, longer-term epidemiological data are available, but there is a paucity of longer-term observational studies of stroke patients reporting cost data. Most economic studies of stroke follow-up patients for 1 or 2 years and use modeling techniques to extrapolate to lifetime costs (10 to 15 years for this population) based on mortality, progression through disability levels over time, and correlations between disability levels and cost. Generally, cost models based on studies with a longer time period of actual patient-specific resource use data will be more reliable.
One implication of greater mortality among patients with AF-related stroke is a reduced population of survivors incurring long-term costs. However, in economic analyses death remains a negative outcome, so the value of more premature deaths avoided (years of life gained) by stroke prevention among AF patients must be realistically incorporated into cost-effectiveness estimates.\textsuperscript{50} The increased recurrence rate associated with AF stroke also has to be accurately represented in economic analyses in terms of additional costs and years of life lost, because recurrent strokes tend to be more severe and more often fatal than first strokes.\textsuperscript{37}

It has been demonstrated that initial stroke severity (not age or comorbidity) is a significant predictor of length of initial hospital stay.\textsuperscript{20,51} In addition, stroke characteristics will influence duration of survival and disability (and consequently the costs of long-term care), whether defined by disease subtype,\textsuperscript{52} Barthel score,\textsuperscript{53} or Rankin score.\textsuperscript{37} Admission to a nursing home, which has a large impact on total cost, is more likely in patients with severe stroke of age 65–100 y. Anticoagulation is most beneficial (prolongation of life at an acceptable cost) in those at major risk for stroke because of previous stroke or transient ischemic attack, diabetes mellitus, and hypertension.

TABLE 3. Studies Estimating the Cost-Effectiveness of Anticoagulation in AF Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>AF Patient Group</th>
<th>Cost-Effectiveness Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustafsson et al (1992)\textsuperscript{42}</td>
<td>VKA or aspirin vs no antithrombotic therapy</td>
<td>Medium risk (1 risk factor for stroke)</td>
<td>Anticoagulation with VKA (or with ASA if contraindications exist) is cost saving</td>
</tr>
<tr>
<td>Eckman et al (1992)\textsuperscript{43}</td>
<td>VKA vs no antithrombotic therapy</td>
<td>AF caused by mitral stenosis</td>
<td>Cost-effectiveness of anticoagulation $3700 per QALY</td>
</tr>
<tr>
<td>Gage et al (1995)\textsuperscript{44}</td>
<td>VKA vs aspirin</td>
<td>High risk (&gt;2 risk factors for stroke)</td>
<td>VKA is dominant (ie, greater quality-adjusted survival and cost-savings)</td>
</tr>
<tr>
<td>Gage et al (1998)\textsuperscript{45}</td>
<td>Patient preference-based therapy (aspirin or VKA) vs VKA for all</td>
<td>Medium risk (1 risk factor for stroke)</td>
<td>VKA cost-effectiveness $8000 per QALY (an excellent use of healthcare resource)</td>
</tr>
<tr>
<td>Lightowlers and McGuire (1998)\textsuperscript{33}</td>
<td>VKA vs no antithrombotic therapy</td>
<td>Various populations</td>
<td>VKA is dominant for patients older than 65 y, and more so for patients older than 75 y</td>
</tr>
<tr>
<td>Thomson et al (2000)\textsuperscript{46}</td>
<td>VKA vs no antithrombotic therapy</td>
<td>Women older than 75 y</td>
<td>VKA is dominant or has an acceptable cost per QALY ratio for:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women aged 65–74 y</td>
<td>97% of patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men older than 75 y</td>
<td>69% of patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men aged 65–74 y</td>
<td>75% of patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>53% of patients</td>
</tr>
<tr>
<td>Desbiens (2002)\textsuperscript{47}</td>
<td>VKA vs no antithrombotic therapy</td>
<td>Age 65–100 y</td>
<td>Anticoagulation is most beneficial (prolongation of life at an acceptable cost) in those at major risk for stroke because of previous stroke or transient ischemic attack, diabetes mellitus, and hypertension</td>
</tr>
<tr>
<td>Samsa et al (2002)\textsuperscript{48}</td>
<td>VKA managed by anticoagulation clinics or patient self-testing/self-management (PST/PSM) vs usual care or no antithrombotic therapy</td>
<td>AF patients &gt;3 mo from start of VKA therapy</td>
<td>Cost-savings are generated by strategies where more eligible patients can receive VKA; PST/PSM and anticoagulation clinics are cost-saving vs usual care and no anticoagulation; PST/PSM saves $1.8 million per 1000 patient-years vs no anticoagulation</td>
</tr>
</tbody>
</table>

VKA indicates vitamin K antagonist (eg, warfarin).

TABLE 4. Distribution of AF-Related Stroke Events Used in Models of the Cost-Effectiveness of Anticoagulation in Patients With AF

<table>
<thead>
<tr>
<th>Study</th>
<th>Severity Data Source</th>
<th>Fatal (%)</th>
<th>Severe (%)</th>
<th>Moderate (%)</th>
<th>Mild (%)</th>
<th>None (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gage et al (1995)\textsuperscript{44}</td>
<td>Anticoagulation trials</td>
<td>24</td>
<td>19</td>
<td>32</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Gage et al (1998)\textsuperscript{45}</td>
<td>Anticoagulation trials</td>
<td>24</td>
<td>19</td>
<td>32</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Lightowlers et al (1998)\textsuperscript{33}</td>
<td>Boston Area Anticoagulation Trial for AF</td>
<td>7</td>
<td>40</td>
<td>53</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Thomson et al (2000)\textsuperscript{46}</td>
<td>Oxfordshire Community Stroke Project</td>
<td>45</td>
<td>23</td>
<td>...</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Desbiens (2002)\textsuperscript{47}</td>
<td>Anticoagulation trials</td>
<td>13–34</td>
<td>78 (with residuals)</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>
Although models assessing the cost-effectiveness of anticoagulation in AF patients use outcome data from AF populations in clinical trials, it is unclear whether the AF-related strokes that occur in these trials are typical (in terms of frequency and severity) of those that occur in real-life clinical practice (eg, anticoagulant intensity may be less well-controlled in real life than in a trial setting; age and comorbidities among the populations may be different). Stroke occurring in patients at subtherapeutic International Normalized Ratio values are more severe than those in patients with a therapeutic intensity of anticoagulation.\textsuperscript{54} Epidemiological studies may be more informative on these issues than clinical trials. Some studies have used the Framingham\textsuperscript{55} or other population data for calculation of the absolute risk of stroke,\textsuperscript{42,46} but Thomson et al\textsuperscript{46} acknowledge that the risk was derived from data from the entire Framingham cohort, not just those with AF, and that regression equations tend to underestimate risk in those at the higher end of the range. Hence, the absolute risk of stroke in patients with AF may be underestimated in their model.

Among the practical limitations of warfarin is its variable anticoagulant effect. The fear of causing bleeding is one reason why anticoagulation is underused, particularly in the most elderly, despite the fact that they generally have the highest risk of stroke. Some investigators have found a higher incidence of bleeding in elderly patients receiving warfarin,\textsuperscript{56} whereas others suggest that more studies are needed that better-estimate the risk of intracranial bleeding with and without anticoagulation.\textsuperscript{37} Most clinical trials of anticoagulation do not include this age group. Therefore, an important part of the research agenda should be to understand the benefit/risk relationship, ideally in a study that includes an economic analysis. If the effectiveness and safety of anticoagulation (whether in usual [ambulatory] care or in an anticoagulation clinic setting) can be demonstrated in this age group, then the economic gain could be further emphasized. The extent of potential underestimation of the unit cost of stroke needs to be explored further, and our key recommendation for new research is to conduct a study to collect long-term costs of stroke in patients with AF (compared with non-AF patients). This would permit new economic analyses on existing raw data from published trials using more specific (presumably higher) cost-of-stroke data. If also applied to new clinical efficacy studies (such as among the elderly or people at lower risk of stroke), it would inform about cost-effectiveness in different groups of patients. This research is urgent because underestimation of the value of anticoagulation will affect clinical practice.

References


Are Cost Benefits of Anticoagulation for Stroke Prevention in Atrial Fibrillation Underestimated?

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