Stroke prophylaxis with warfarin or dabigatran for patients with non-valvular atrial fibrillation-cost analysis

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Abstract

Background: cost of anticoagulation with dabigatran is largely based on estimation of complication rates derived from clinical trials.

Objective: to investigate cost of anticoagulation with dabigatran in comparison with warfarin in clinical practice.

Methods: a prospective observational study of patients with non-valvular atrial fibrillation (NVAF) referred to anticoagulation clinic. Patients were interviewed (4–6 weekly by telephone) about bleeding events. Costs of anticoagulation were calculated as: (i) drug cost, (ii) international normalised ratio (INR) monitoring cost and (iii) bleeding cost. For cost calculation of dabigatran, INR monitoring cost was omitted.

Results: a total of 402 patients were included and followed up for a mean (SD) of 19 (8.1) months. Annual cost of anticoagulation was £207.3 and £1,573.5 per patient for warfarin and dabigatran, respectively. Drug price constituted 13.6% of the total cost for warfarin and 94% for dabigatran. Total cost of anticoagulation to prevent one stroke per year was £6,219, £28,086.5 and £25,181 for warfarin, dabigatran 110 and 150 mg, respectively.

Conclusion: cost of anticoagulation is mainly driven by drug price for dabigatran and quality of INR control for warfarin. Until the price of dabigatran is reviewed, warfarin remains suitable for the majority of patients with NVAF.

: anticoagulation, non-valvular atrial fibrillation, cost

Introduction

Non-valvular atrial fibrillation (NVAF) is the most common sustained cardiac arrhythmia [1]. It increases risk of ischaemic stroke by fivefold [2]. Anticoagulation with warfarin reduces this risk by two-thirds [3]. However, warfarin treatment can be problematic with inconvenience of frequent blood testing, narrow therapeutic range of the international normalised ratio (INR) and risk of bleeding. This has resulted in an under utilisation of warfarin in approximately a third of eligible patients with NVAF [4]. Newer anticoagulants, such as dabigatran (direct thrombin inhibitor), have been shown to be as effective as warfarin at stroke prevention, incurring similar or lower bleeding complications without imparting the inconveniences
of INR monitoring and dose adjustment [5]. However, cost implications of replacing warfarin with dabigatran are still unclear. Current cost analysis of dabigatran in comparison with warfarin is largely based on estimation of complication rates and quality of anticoagulation control derived from clinical trials [6]. There is little literature investigating actual clinical practice costs. We previously investigated cost implications of warfarin use for stroke prophylaxis in a real-life situation of clinical practice [7]. We have repeated the analysis with assumption that our cohort was taking dabigatran instead of warfarin deducting away the costs of INR monitoring and comparing the costs of the two anticoagulants in stroke prevention.

Methods

Design
A prospective observational study.

Population and setting
The study was conducted between November 1999 and July 2001 and detailed methodology was previously described [7]. All patients with NVAF newly referred to anticoagulation clinic were included. At the initial clinic visit, demographic data were collected including age, sex, employment status, past medical history and medications. Patients were followed up by telephone interview every 4–6 weeks for up to 31 months. They were questioned about bleeding events, bleeding-related physician visits or hospital attendance. For patients with cognitive dysfunction, caregivers were interviewed. Minor bleeding was defined as bleeding not requiring medical intervention; and major bleeding as any bleeding leading to hospital admission, emergency procedure or blood transfusion. Medical notes were reviewed and general practitioners were contacted for patients who reported bleeding requiring either physician visit or hospital admission for confirmation. At the last interview, patients were asked about their perception of warfarin therapy. We have compared our cohort stroke risk and outcomes with the recently published ‘The Randomized Evaluation of Long Term Anticoagulation Therapy’ (RE-LY) [5] study to assure relevance to the current population.

Cost calculation
Costs of anticoagulation were calculated based on: (i) drug cost, (ii) INR monitoring cost (blood tests, transport, district nurse visits for blood sampling, time off work for patient and carer and postage of INR results) and (iii) bleeding complications costs (physician visits or hospital admission costs). The costs were abstracted from the National Health Service (NHS) reference costs for the year 1999–2000, Financial Development Branch, NHS Executive (UK). The cost of anticoagulation to prevent one stroke per year was calculated by multiplying costs of anticoagulation of one patient per year by number of patients needed to treat (NNT) to prevent one stroke. Using data from the office of national statistics, the costs incurred in the year 1999–2000 were multiplied by a factor of 1.3 to correct for the inflation for the current year 2011 [8].

Dabigatran cost
We have repeated the analysis with the assumption that our cohort was given dabigatran instead of warfarin. As a result, we have omitted the costs of INR monitoring and kept the bleeding complication costs similar to warfarin.

Statistical analysis
We have used the statistical software package ‘Stata version 10’, StataCorp LP, College station, TX, USA in data analysis.

Results

Baseline characteristics and bleeding events
A total of 402 new NVAF patients were included and followed up for a mean (SD) of 19 (8.1) months, range 1.0–31.0 months, equivalent to 634 patient-years of treatment. The mean (SD) age was 72.3 (10.3), range 34–94 years, 199 (50%) were ≥75 years old and 178 (44%) were women. Twenty-two (6%) patients died during follow-up with no bleeding-related mortality. Bleeding events occurred in 100 patients (11 major and 89 minor bleeding). The annual event rates were 1.7% (95% confidence interval 0.4–3.0) for major bleeding and 16.6% (13.0–20.2) for minor bleeding. Comparison with the RE-LY study is detailed in Table 1.

Anticoagulation monitoring and cost
A total of 9,826 INR tests were performed during the study period [mean (SD) of 24 (14.9) tests per patient]. Mean (SD) time spent in target INR (2–3) was 66% (20.2) for minor bleeding and 66% (20.2) for minor bleeding per year (Table 2). Based on NNT of 30, 29 and 26 patients for warfarin, dabigatran 110 and 150 mg (derived from RE-LY study outcomes) [5], the total cost of anticoagulation to prevent one stroke per year is £6,219, 28,086.5 and £25,181, respectively.

Discussion
We have calculated the actual day-to-day costs of anticoagulation with warfarin versus dabigatran. Our population, although recruited 10 years ago, their stroke risk and outcomes are comparable with the RE-LY study. We had more women but this could be due to that our cohort was...
Stroke prophylaxis with warfarin or dabigatran for patients with non-valvular atrial fibrillation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Current study</th>
<th>RE-LY study</th>
<th>Difference, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>402</td>
<td>18,113</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age</td>
<td>72.3 (10.3)</td>
<td>71.5 (8.8)</td>
<td>0.8 (--0.2 to 1.8)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>178 (44)</td>
<td>6,599 (36)</td>
<td>8% (3 to 13)</td>
</tr>
<tr>
<td>History of stroke or TIA</td>
<td>98 (24)</td>
<td>2,428 (20)</td>
<td>4% (--1 to 8)</td>
</tr>
<tr>
<td>CHADS2 score</td>
<td>2.14 (1.1)</td>
<td>2.13 (1.1)</td>
<td>0.01 (--0.1 to 0.1)</td>
</tr>
<tr>
<td>0−1 (%)</td>
<td>31</td>
<td>32</td>
<td>1% (--1 to 7)</td>
</tr>
<tr>
<td>2 (%)</td>
<td>35</td>
<td>36</td>
<td>1% (--1 to 6)</td>
</tr>
<tr>
<td>3−6 (%)</td>
<td>34</td>
<td>32</td>
<td>2% (--3 to 6)</td>
</tr>
<tr>
<td>Outcomes (annual rate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All TEE (%)</td>
<td>1.5</td>
<td>1.4</td>
<td>0.1% (--0.7 to 1.8)</td>
</tr>
<tr>
<td>All bleeding (%)</td>
<td>18.3</td>
<td>16.4</td>
<td>1.9% (--1.5 to 6)</td>
</tr>
<tr>
<td>All cause mortality (%)</td>
<td>3.4</td>
<td>3.8</td>
<td>0.4% (--2 to 1.7)</td>
</tr>
</tbody>
</table>

CI, confidence interval; TIA, transient ischaemic attack; CHADS2, A stroke risk score with one point for a history of congestive cardiac failure, hypertension, age ≥75 years or diabetes mellitus and two points for a history of stroke or TIA. Total score is the sum of all points [12]. TEE, thromboembolic events.

### Table 2. Actual cost (£) of anticoagulation (adjusted for year 2011) per patient per year

<table>
<thead>
<tr>
<th>Cost category</th>
<th>Warfarin</th>
<th>Dabigatran, 110 mg bd</th>
<th>Dabigatran, 150 mg bd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug (per cent of total cost)</td>
<td>28.2 (13.6)</td>
<td>907 (94)</td>
<td>907 (94)</td>
</tr>
<tr>
<td>Monitoring (per cent of total cost)</td>
<td>117.6 (56.7)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>INR</td>
<td>72.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Travel</td>
<td>33.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time off work</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurse visits</td>
<td>6.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postage</td>
<td>3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications (per cent of total cost)</td>
<td>61.5 (29.7)</td>
<td>61.5 (6)</td>
<td>61.5 (6)</td>
</tr>
<tr>
<td>Physician's visits</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>59.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>207.3</td>
<td>968.5</td>
<td>968.5</td>
</tr>
<tr>
<td>Cost to prevent one stroke per year*</td>
<td>6,219</td>
<td>28,086.5</td>
<td>25,181</td>
</tr>
</tbody>
</table>

*Based on number needed to treat of 30, 29 and 26 patients, respectively, for warfarin or dabigatran 110 mg and dabigatran 150 mg. The cost of dabigatran was calculated at £75.6 per month for both doses (excluding tax) as stated in the recent National Institute of Clinical Excellence (NICE) appraisal [10].

slightly older. It is likely that our cost adjustment for 2011 value is accurate. For example, our annual INR monitoring cost of £117.6 is similar to the recent National Institute of Clinical Excellence (NICE) estimation of £115.14 [9]. This analysis has shown that drug price constitutes 13.6% (warfarin) and 94% (dabigatran), respectively, of the total costs of anticoagulation. The cost of dabigatran to prevent one stroke per year was about four to five times that of warfarin. In a recent cost-effectiveness analysis in a hypothetical cohort of 70-year-old patients with NVAF, warfarin was cost-effective in stroke prevention in moderate-risk patients unless risk of haemorrhage was high or quality of INR control was poor [time in the therapeutic range (TITR) <57.1%]. For patients with a high stroke risk, dabigatran 150 mg was cost-effective unless INR control was excellent (TITR >72.6%). Dabigatran 110 mg was not cost-effective [6]. These data suggest that cost-effectiveness of warfarin is dependent on quality of INR control and this may vary from one centre to another. Freeman et al. have found that dabigatran 150 mg was the most cost-effective dose compared with warfarin in older people (>65 years) based on the RE-LY study [10]. However, relative effectiveness of dabigatran versus warfarin was seen at centres with poorer INR control while in centres with good INR control the relative effectiveness and safety of dabigatran was almost the same as with warfarin [11]. In our cohort anticoagulation control was good as patients spent 66% of the time in target INR (2−3). We may slightly have over estimated bleeding costs for dabigatran 110 mg but this is likely to be marginal as complication constitutes only 6% of the total cost. The net clinical benefits of the two doses of dabigatran were similar in the RE-LY study because of the lower risk of ischaemia with 150 mg and lower risk of haemorrhage with 110 mg. The overall advantages expected from dabigatran were increased efficacy, lower bleeding and no monitoring which may have a positive impact on quality of life. However, there are several factors that could have a negative effect on patients’ compliance such as its twice daily dosing and side-effects. In RE-LY study rates of discontinuation for dabigatran (110 mg), dabigatran (150 mg) and warfarin were 14.5, 15.5 and 10.2%, respectively, at 1 year and 20.7, 21.2 and 16.6% at 2 years (P < 0.001). This was due to serious adverse events with dabigatran especially gastrointestinal (gastric pain, vomiting and diarrhoea compared with warfarin, P < 0.001). Dyspepsia occurred in 5.8% of patients in the warfarin group, 11.8 and 11.3% in patients on dabigatran 110 and 150 mg, respectively (P < 0.001). There was a significantly higher rate of major gastrointestinal bleeding with dabigatran (150 mg) than with warfarin. Therefore, safety of dabigatran in patients with a history of peptic ulcer disease remains unknown. It should also be noted that there is a trend towards increased rates of myocardial infarction with dabigatran [5]. The most important advantage of dabigatran was the lower rate of intracranial bleeding than warfarin, 0.23, 0.3 and 0.74% for dabigatran (110 mg), (150 mg) and warfarin, respectively. Although INR monitoring may be perceived as troublesome, patient perception of warfarin treatment in our cohort was generally positive with 97% of patients did not worry much about frequent blood testing. INR monitoring may also be useful for evidence of patient compliance. Other advantage of warfarin is that there is an antidote should major bleeding occurs.

### Conclusion

The cost of anticoagulation is mainly driven by drug price for dabigatran and quality of INR control for warfarin. At
present dabigatran may be suitable for patients with high stroke and bleeding risks such as frail older people with multiple comorbidities and polypharmacy in whom anticoagulation control is erratic or monitoring is not feasible. Until the price of dabigatran is reviewed, warfarin remains suitable for the majority of patients with NV AF.

Key points

- Cost of anticoagulation is largely driven by drug price for dabigatran and quality of INR control for warfarin.
- Cost of dabigatran to prevent one stroke per year is about four to five times that of warfarin.
- Majority of patients on warfarin therapy are not troubled by frequent blood testing.

References


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The frailty index in Europeans: association with age and mortality

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Abstract

Background: the frailty index (FI) is an approach to the operationalisation of frailty based on accumulation of deficits. It has been less studied in Europeans.

Objective: to construct sex-specific FIs from a large sample of Europeans and study their associations with age and mortality.