Dabigatran in atrial fibrillation: incremental benefit over a time horizon of 5 or 10 years
Andrea Messori, Valeria Fadda, Dario Maratea and Sabrina Trippoli

The cost effectiveness of dabigatran in atrial fibrillation in comparison with warfarin has previously been evaluated by studies in which the time horizon was either lifetime or projected over 20–35 years. In these analyses, an incremental benefit varying from 1.75 to 6.72 quality-adjusted life months (QALMs) per patient has been reported. In our study, we determined the incremental benefit of dabigatran (150 mg twice daily) by restricting the time horizon to only 5 or 10 years. The base-case population (patients with atrial fibrillation at risk for stroke) was assumed to be aged 65 years. The analysis was carried out using Markov modelling. Benefits were discounted at 3% yearly. Our analysis based on 10-year horizon showed a gain of 2.24 QALMs per patient. Using the 5-year horizon, the incremental benefit was 0.88 QALMs per patient. As regards the economic implications of these results, a benefit of around 0.88 QALMs per patient (with 5-year or 10-year horizon, respectively) indicates that an ‘acceptable’ cost of the treatment is around €1000 per year. This simplified assessment (which refers to the commonly used threshold of €5000 per QALM gained) does not incorporate any recognition of the savings in terms of reduced cost-of-illness.

The treatment cost in the United Kingdom is within this range. In most of the other countries, the price of dabigatran for atrial fibrillation has not yet been negotiated.

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Letter to the editor
In Europe, several national drug agencies (including the Italian one) are examining the issue of whether new oral anticoagulants such as dabigatran or rivaroxaban can be reimbursed for atrial fibrillation. In making this decision, the main question is of economic nature; for example, Gage1 has estimated that ‘if all of the approximately 760 000 British patients with atrial fibrillation took dabigatran at GBP 919.80 (€1051; $1471) per year, the drug cost would be £700m each year’.

The cost effectiveness of dabigatran in atrial fibrillation has been studied in 2011 by four reports2–5 that examined both cost and benefits in comparison with warfarin. The time horizon of these analyses was either lifetime2,3 or projected over 204 or 355 years. The magnitude of the incremental benefit of dabigatran 150 mg twice daily versus warfarin, expressed in quality-adjusted life years (QALYs), was found to be 0.146 QALYs per patient,2 0.180 QALYs per patient,3 0.250 QALYs per patient,4 and 0.560 QALYs per patient5; the corresponding values expressed as quality-adjusted life months (QALMs) are 1.75, 2.16, 3.0, and 6.72 QALMs per patient.

The results of these studies (in particular, those of Pink et al.,2 Sorensen et al.,3 and Shah and Gage1) offer a relatively homogeneous picture of the long-term benefit expected from dabigatran 150 mg twice daily in comparison with warfarin (with small between-study differences in the incremental benefit and a quite restricted age range of the population examined). However, one point of controversy is that ‘clinicians may feel uncomfortable extrapolating from a 2-year trial to a lifetime horizon’1; this is because extending the perspective of these assessments over decades increases their level of uncertainty.

In the present analysis, we determined the projected benefits of dabigatran 150 mg twice daily in comparison with warfarin by restricting the time horizon of our analysis to only 5 or 10 years as opposed to the lifetime (or very long-term) perspective employed in the previous studies. Our study was meant to be an extended sensitivity analysis with regard to the results presented in previously studies2–5 and was specifically aimed at assessing the incremental benefit over a shorter time horizon. Focusing on the benefit (and on the time needed to achieve it) is because these two variables are the main determinant of the incremental cost-effectiveness ratio of dabigatran, along with the drug cost.

Our analysis compared dabigatran 150 mg twice daily (denoted as high-dose dabigatran) versus warfarin by estimating the value of QALYs over 5 or 10 years. The transition probabilities incorporated in our model are shown in Fig. 1. The base-case population (patients with atrial fibrillation at risk for stroke) was assumed to be aged 65 years. The analysis was carried out using Markov modelling. Benefits were discounted at 3% yearly. Our analysis based on 10-year horizon showed a gain of 0.88 QALMs per patient. Using the 5-year horizon, the incremental benefit was 0.25 QALMs per patient. As regards the economic implications of these results, a benefit of around 0.25 QALMs per patient (with 5-year or 10-year horizon, respectively) indicates that an ‘acceptable’ cost of the treatment is around €1000 per year. This simplified assessment (which refers to the commonly used threshold of €5000 per QALM gained) does not incorporate any recognition of the savings in terms of reduced cost-of-illness.

The treatment cost in the United Kingdom is within this range. In most of the other countries, the price of dabigatran for atrial fibrillation has not yet been negotiated.
We employed the same Markov simulation model described by Freeman et al.\(^5\) with the following exceptions: since the original paper of these authors did not report sufficient details for some minor parameters, the following data represent the information that we drew from other sources: a) the transition probability of the three final branches of the ICH branch in Panel B (namely, 0.09, 0.46 and 0.45) that we took from Table 4 of Sorensen et al.;\(^3\) b) the demographic estimates of life-expectancy for people aged more than 65 years that we took from Table 1 of reference.\(^9\) ICH, intracranial haemorrhage; RIND, reversible ischaemic neurologic event; TIA, transient ischaemic attack.

The model described by Freeman et al.\(^5\) has been re-adapted to run our analysis over a time horizon of 5 or 10 years. Panel A shows the first markovian node (with the ‘Well’ state and 8 terminal states) while Panel B shows all of the various branches departing from the ‘Well’ state. Numbers associated with each state represent the respective transition probability. In Panel B, the probabilities refer to patients treated with warfarin; in the case of treatment with high-dose dabigatran, the four probabilities of 0.00467, 0.0120, 0.0074, and 0.0053 shown in Panel B are replaced with 0.00358, 0.0092, 0.0030, and 0.0074, respectively. All of these transition probabilities have been reported by Freeman et al.\(^5\) with the following exceptions: since the original paper of these authors did not report sufficient details for some minor parameters, the following data represent the information that we drew from other sources: a) the transition probability of the three final branches of the ICH branch in Panel B (namely, 0.09, 0.46 and 0.45) that we took from Table 4 of Sorensen et al.;\(^3\) b) the demographic estimates of life-expectancy for people aged more than 65 years that we took from Table 1 of reference.\(^9\) ICH, intracranial haemorrhage; RIND, reversible ischaemic neurologic event; TIA, transient ischaemic attack.

The results of our primary analysis (horizon, 10 years; discounting, 3% per year) showed a value of 7.913 QALYs per patient for high-dose dabigatran versus 7.726 QALYs per patient for warfarin; the gain was 2.24 QALMs per patient (or 0.187 QALYs). Likewise, the undiscounted analysis based on the same horizon estimated 8.827 QALYs per patient for dabigatran 150 mg twice daily versus 8.610 QALYs per patient for warfarin with a gain of 2.61 QALMs per patient (or 0.217 QALYs). Use of the 5-year time horizon gave an incremental benefit of 0.8844 (discounted) and 0.9420 (undiscounted) QALMs per patient (i.e., 0.0737 and 0.0785 QALYs, respectively).

Table 1 summarizes the main findings of our study in comparison with those reported by previous cost-effectiveness articles in this area. These estimates of the incremental benefit (around 2.5 QALMs with 10-year horizon; less than 1 QALM with 5-year horizon) emphasize the small magnitude of the incremental benefit of dabigatran. This finding, however, is shared by the majority of current innovative agents aimed at other disease conditions; for example, the median gain estimated from the analysis of 37 innovative anticancer
Table 1  Comparison of the results of our analysis with those published in four studies published in 2011

<table>
<thead>
<tr>
<th>Study (first author)</th>
<th>Age (years)</th>
<th>Gain for the comparison of high-dose dabigatran versus warfarin (QALMs per patient)</th>
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<td>Present study</td>
<td>65</td>
<td>0.8844 (with 3% discounting), 0.9420 (undiscounted), 2.24 (with 3% discounting), 2.61 (undiscounted)</td>
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<td>Pink a</td>
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<td>Sorensen SV, Kansal AR, Connolly S, et al. b</td>
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<td>Shah a</td>
<td>70</td>
<td>–</td>
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<tr>
<td>Freeman JV, Zhu RP, Owens DK, et al. b</td>
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QALMs, quality-adjusted life months. a The study by Freeman et al. should be regarded as lifetime because their population (aged 65 years) was projected until the age of 100 years. b These gains are the base-case difference between high-dose dabigatran and warfarin according to the following treatment specific values: 6.536 versus 6.390 QALMs for ref. 2, 6.68 versus 6.68 for ref. 3, 8.65 versus 8.43 for ref. 5, and 10.84 versus 10.28 QALMs for ref. 5.

agents was only 2.0 QALMs per patient (range: 0.09–18.0 QALMs).

As regards the economic implications of these results, one can make reference to the threshold of €5000 per QALM gained (or €60 000 per QALY gained) which is frequently employed for reimbursement decisions in Europe (especially in Italy). A benefit of around 2.5 QALMs (with 10-year horizon) or less than 1 QALM (with 5-year horizon) can be converted into an ‘acceptable’ cost of the treatment around €1000 per year (in detail: €884 to €942 with 5-year modelling and €1120 to €1305 with 10-year modelling).

This simplified assessment, that does not incorporate any recognition of the savings in terms of reduced cost-of-illness, indicates that this treatment should be reimbursed at a maximum yearly cost of €884 to €1305 per patient. The treatment cost in the United Kingdom is within this range; in the other countries, the price of dabigatran for atrial fibrillation has not yet been negotiated.

In general, the results of cost-effectiveness studies obtained through a complex modelling process cannot be easily transferred from one jurisdiction to another or from one country to another. In this case, transferring the results of the four cost-effectiveness studies mentioned above to a specific country would require a substantial readaptation of the model or at least refocusing the model with country-specific unit cost parameters (including the drug price), an information that is not readily available.

On the contrary, empiric decisions by regulatory agencies or by third payers are often based on the analysis of the incremental clinical benefit and on value-based pricing wherein prices are proportional to clinical benefits; in contrast, a full recognition of the reduced expenditure in terms of cost-of-illness is much less frequent, at least in Italy.

In conclusion, our analysis indicates that the incremental benefit of dabigatran takes place to a not negligible extent also in the initial 5 or 10 years and suggests a yearly cost for this treatment based exclusively on this information. These simplified analyses (see also Fojo and Grady) are a reasonable compromise between fully empiric decisions on the reimbursability of new treatments and the use of very complex modelling techniques that are not presently employed by most European drug regulatory agencies.

Acknowledgements
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References
1 Gage BF. Cost of dabigatran for atrial fibrillation. BMJ 2011; 343:d6980 (Published 31 October 2011).
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In the legend to Fig. 1, our original manuscript contained an error because the first group of 4 probabilities and the second group of 4 probabilities were erroneously exchanged with one another. To better clarify this correction in the enclosed proofs, we have re-written all the 8 values but the correction needed is simply to exchange the first group with the second.
Research Letter

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The results of these studies (in particular, those of Pilk et al.7, 8 Sorensen et al.2 and Shah and Gage10) offer a relatively homogeneous picture of the long-term benefit expected from dabigatran 150 mg twice daily in comparison with warfarin (with small between-study differences in the incremental benefit and a quite restricted age range of the population examined). However, one point of controversy is that 'clinicians may feel uncomfortable extrapolating from a 2-year trial to a lifetime horizon'; this is because extending the perspective of these assessments over decades increases their level of uncertainty.

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65 years as in Freeman’s study. We employed the same Markov simulation model described by Freeman et al., some changes were introduced to manage a few minor characteristics of the model that the original report did not describe in sufficient detail to allow us to reproduce them (see footnote 11). Benefits were discounted at 3% yearly as in Freeman’s study, but also an undiscounted analysis was carried out. Dabigatran 110 mg twice daily was not examined mainly because this dosage has not been approved by the Food and Drug Administration (FDA). All calculations were performed using TreeAgePro (TreeAge Software Inc., Williamstown, Massachusetts, USA).

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