PREFACE

This article was written by Mia Buus Andersen during fourth semester of Medical Market Access in Medicine with Industrial Specialisation, Department of Health Science and Technology, Aalborg University, Denmark. The idea behind this project was developed in cooperation with "Forskningens Hus" at Aalborg Hospital. After completion, it is of purpose that this article will be used for further study on the subject. For all price calculations, Marevan® was used for warfarin and Pradaxa® for dabigatran.

I would like to thank Lars Oddershede, PhD student and Lars H. Ehlers, Professor in the Department of Economy and Management at Aalborg University, for guidance and theoretical advice during the project period. Furthermore I would like to thank Morten Jensen, Morten Juhl and Felicia Spector for graphic and linguistic guidance.

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Project period:	1st of February to 31th of May 2012
Project group:	12gr1000
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Numbers printed:	4
Number of pages:	13

Cost Effectiveness of a New Oral Anticoagulation Drug for Stroke Prevention in AF Patients

- A Decision Analysis of Dabigatran

Mia Buus Andersen, Master Thesis, Medical Market Access, Aalborg University 2012

Key words: atrial fibrillation, stroke, warfarin, dabigatran, hemorrhage, cost-effectiveness, disutility

Background - Contemporary management of stroke prevention in patients with atrial fibrillation (AF) imposes several challenges, such as drug-drug interactions, drug-food interactions, regular control of international normalised ratio (INR), and hemorrhagic events. This analysis investigates the cost-effectiveness of a new oral anticoagulation (NOAC) drug, which was reported to be a safer and easier drug, as an alternative for warfarin.

Methods - A Markov decision tree was designed for calculation of cost effective ratio for time span of 1, 2, 5 and 26 years, with the perspective of the Danish health care system as a payer. An utilisation of data reported from RE-LY study was converted into Danish settings. Costs and QALY outcome was based on Danish tariffs and best evidence in literature. One-way analysis and probabilistic sensitivity analysis (PSA) was conducted to evaluate robustness of results obtained.

Results - At base case conditions, the cost effectiveness ratio after the first year was estimated to £ 50969,98 GBP per quality adjusted life year (QALY). After year one, the cost effectiveness ratios showed that dabigatran might be a cost effective alternative, given the set-up of Markov model premises. One-way analysis revealed that key parameters were subjects to uncertainty.

Conclusion - This analysis suggests that, with a lifetime perspective, the new anticoagulation drug dabigatran might be a cost effective approach for stroke prophylaxis for patients with diagnosed AF and a $CHADS_2$ score of 1≤, when compared to the standard. However, these results must be taken with caution, as the analysis was based on non-Danish settings and conservative approaches were taken.

Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia, affecting approximately 6 % of the Danish population above the age of 65 [1-5]. In 2011, >50,000 patients were diagnosed with AF, which has been estimated to increase to 150,000 by the end of 2050 [6].

AF has the potential for serious consequences for patients, due to an increase in morbidity mainly due to a four-fold increased risk of stroke and systemic embolism [7]. AF may additionally reduce quality of life, functional status and cardiac performance [7-9]. It is associated with high medical costs for the Danish health care system as well as an increased risk of death, laying a burden on the yearly fiscal constraints [10-12]. With the mean population age increasing, a rise in AF patients is expected, and thereby an even higher burden on the health care budget [13].

$CHADS_2$ score: clinical prediction rule for estimating the risk of stroke in AF patients. It is used to determine if anticoagulation therapy is required. A score below 1 does not require anticoagulant treatment. Increase in score is corresponding with increase in risk of stroke.

INR level: international normalised ratio, used for measuring the time of bloods ability to coagulate. For AF patients, a level of 2.0-3.0 is accepted as stable, but preferred around 1.0.

The usage of warfarin, a vitamin K antagonist, has for several decades proven its effectiveness in stroke reduction in practice as well in several randomised trials [14-16]. However, warfarin has a narrow therapeutic window and may fail to prevent stroke or lead to serious hemorrhagic events if anticoagulation is inadequate [15,17]. Interaction of vitamin K antagonist with food, drugs, and several other factors, requires dose adjustments and regular monitoring of international normalised ratio (INR) level. The inconvenience of warfarin associated with unpredictability, contributes to extreme under treatment of high-risk AF patients in Scandinavian [18]. As a result of these limitations, new oral anticoagulation has been developed to make up for these difficulties.

Dabigatran, a novel oral direct thrombin inhibitor, was recently approved by the Danish Medicine Agency (National Board of Health), for AF patients with $CHADS_2$ scores of 1≤ [19]. With its profile, it is predictable and stable over time, and has a low potential for drug-drug interactions, as well as drug-food interactions, making INR controlling and dose adjustments unnecessary. The development of dabigatran was initially to generate an equally efficient drug that was safer and easier to administer [20,21].

The approval of dabigatran was based on RE-LY, a phase III trial. This randomised trial incorporated >18,000 AF patients from 44 different counties, and investigated the efficacy and safety of dabigatran in two doses compared with warfarin, adjusted to INR value. The RE-LY study proved that dabigatran was efficient in reducing the risk of stroke and, additionally, the risk of hemorrhagic events [22-24].

With an estimated increase in prevalence of AF patients and the cumbersomeness of warfarin, it is the purpose of this analysis to investigate which stroke prevention drug represents the best value monetarily for the Danish health care system.

METHOD

A decision analytic model was constructed in order to describe possible effects and cost of two different treatment strategies for patients with AF in relation to risk of adverse events over 1, 2, 5 years and life time perspective. The study was based on the RE-LY study and was to address the issue of generalising the RE-LY study to Danish settings, from a health care perspective [22]. The ingredients of the data from RE-LY are introduced by the use of a Markov model to estimate the incremental cost effectiveness ratio (ICER) of dabigatran as an alternative to the current treatment standard.

The study was based on best available data, and conducted in accordance with international guidelines for health economic evaluations [25-29].

All costs are in 2011-2012 levels, and based on PLO collective agreements or the Danish case mix system, dkDRG [30,31]. All unit prices of cost were collected in Danish crowns (DKK) and adjusted to fiscal year 2012 DKK. Subsequently, costs were converted into British Pound (GBP) at fiscal year 2012, using an exchange rate of 8.89DKK/1GBP [32].

THE MARKOV MODEL

The base case model consisted of a hypothetical cohort of patients having AF diagnosed as a chronic disease. The cohort was at the age 65 and a $CHADS_2$ score of ≥1. No distinguishing between man and woman was used in the cohort.

AF patients were able to move through six health states; well with AF on medication, disabled due to stroke, disabled due to major haemorrhage (MH), disabled due to myocardial infarct (MI), disabled due to pulmonary embolism (PE), and death of any causes. For all-cause mortality, an age specific standardised mortality table for men and women was derived from StatBank Denmark [33]. Average mortality adjusted to age was added with a factor 2.0 for patients receiving warfarin and factor 1.98 for dabigatran, in accordance with best available evidence [4,22,23,33]. At baseline, all AF patients were assumed to be in the "well with AF on medication" state.

Markov subtrees with identical structures were used to model the event rate associated with the two treatment strategies, as illustrated in figure 1. The probability of each event was based on the RE-LY study by Connolly et al., and converted into an annual probability [22,23,26].

The Markov cycle length was fixed at one year with utilities and costs adjusted to reflect the cycle length. The results of the analysis were reported for 1, 2, 5 years, and with lifetime perspective (26 years).

For a lifetime perspective the model was constructed with a total of 26 cycles, with patients assumed to reach 100% absorbing state after 25 years, corresponding to all being dead at the age 91 [33]. It was intentionally assumed that patients only have one adverse event during each cycle. Patients on warfarin were estimated to a daily dose of 2.5 mg twice daily, while dabigatran was fixed to 150 mg twice daily, in accordance with the recommendation for patients under the age of 80 [34].

Outcomes were expressed as quality adjusted life years (QALY) for AF patients with an age of 65 years at the starting point of the analysis (no distinction between men and woman). QALY were obtained by a multiplication of the appropriate probability in different health states with the utility estimate for each health state.

Costs were discounted at a rate of 3.5 % beyond the first year [25]. Tracker was added in order to trace the progress of the hypothetical patients different histories during the cycles, data not reported [35].

The Markov model was built and analysed in TreeAge Pro Healthcare 2011(TreeAge Software, Inc, Williamstown, Mass.)

DATA INPUT, COST

This study applies a health care perspective and is therefore limited to health care costs directly linked to medicine, hospital treatment, tests and follow-up visits at a general practitioner. It was assumed that loss attributable to the inability of working due to adverse event would be captured in the disutility of QALY, therefore indirect costs were not included as to evade double counting [27]. All cost concerning rehabilitation and long-term costs of adverse event for AF patients was not included as data was not obtainable for Danish settings.

In the model, different costs are associated with receiving warfarin and the new treatment drug, respectively. Costs were divided into transitional costs and incremental cost. Incremental costs were composed of cost of drug, cost of test for INR at local practitioner and follow up on test by phone. For those receiving warfarin a yearly assumed of 12 visits for INR control with 12 follow-up telephone consultations was set as the base-case standard, see table 1. For patients receiving dabigatran, it was estimated that AF patients have an INR consultation three times yearly, with three follow-up consultations by phone. Further, it was assumed that a s-creatinine test was performed once yearly, as patients with low renal function are in danger when administered with dabigatran [36].

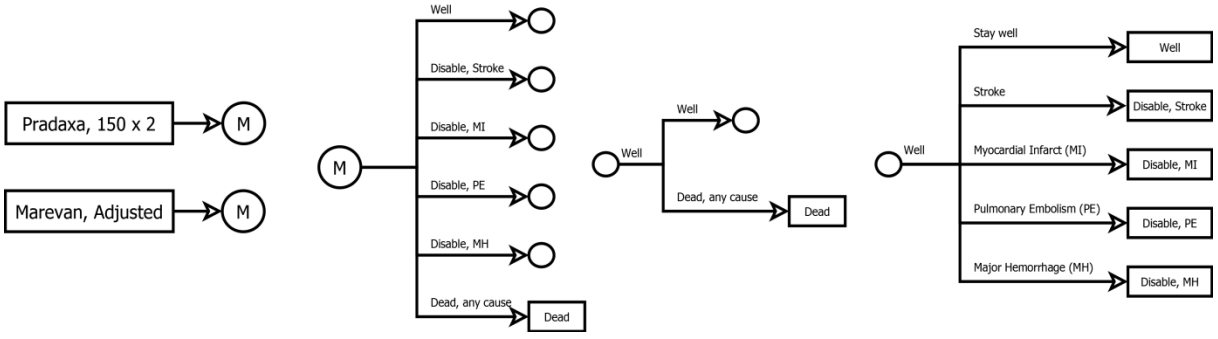

Figure 1: Representation of the Markov model. The two treatment options for patients with atrial fibrillation (AF) are shown on the left. M represent a Markov process with six different health states at a cycle length of one year. All patients remain at the well state during the first year, until adverse events occur. Event for the different states depends on treatment, as well as second adverse event (after year 1). Above figure represents these events for the "well with AF on medication" state. Branches for other health states have similar structure, however another adverse displaces "stay well" event. Dead represent the absorbing state. MI indicates myocardial infarct, PE - pulmonary embolism, MH - major haemorrhage. Pradaxa® correspond to dabigatran and Marevan® to warfarin. Graphic work was composed in DIA version 0.97.2 (Free Software Foundation, Boston USA).

INPUT VARIABLE, PROBABILITY	WARFARIN 2.5MG.x2	DABIGATRAN 150MGx2	REF.
Annual rate for stroke (%)	1.67 (1.2-2.14)	1.05 (0.58-1.52)	[22, 23, 33]
Annual rate for 2nd stroke (%)	2.09 (1.95-2.15)	1.31 (1.24-1.38)	[22, 23, 37]
Annual rate of MI (%)	0.67 (0.40-0.90)	0.83 (0.59-1.07)	[22, 23]
Annual rate of 2nd MI (%)	0.74 (0.70-0.78)	0.91 (0.86-0.96)	[38
Annual rate of PE (%)	0.09 (0.08-0.10)	0.15 (0.14-0.16)	[22, 23]
Annual rate of 2nd PE (%)	0.10 (0.09-0.11)	0.16 (0.15-0.17)	[22, 23, 39]
Annual rate of MH (%)	3.85 (1.90-10.40)	3.47 (1.59-8.98)	[22, 23, 47]+SI, DJ
Annual rate of death (%)	2.99 (1.50-4.59)	2.34 (1.50-3.94)	[4, 12, 22, 23, 33, 48]
INPUT VARIABLE, UTILITY (QALY)			
Healthy individual, age 65	0.861	0.861	[27, 40]
Well w. AF on medication	0.848 (0.806-0.890)	0.855 (0.812-0.897)	[14, 41, 42, 43]
Stroke, all	0.388 (0.369-0.407)	0.395 (0.375-0.415)	[49,50]
MI, all	0.628(0.597-0.659)	0.635 (0.603-0.667)	[51]
PE, all	0.664 (0.631-0.697)	0.701 (0.666-0.736)	[52]
MH, all	0.661 (0.628-0.694)	0.661 (0.628-0.694)	[53]
Dead of any cause	0	0	[27]
INPUT VARIABLE, COST (GBP)			
Yearly cost of medication	114.14 (91.31-136.97)	1026.43 (821.14-1229.72)	[54]
Yearly cost of INR control	80.04 (0-160.89)	20.01 (0-40.02)	[30]
Yearly cost of follow-up	33.53 (0-67.06)	8.38 (0-13.97)	[30]
One time cost of stroke	9571.43 (9092.86-10050)	9571.43 (9092.86-10050)	[31]
One time cost of MI	2665.69 (2268.73 - 6474.24)	2665.69 (2268.73 - 6474.24)	[31]
One time cost of PE	4467.49 (4244.12 - 4690. 86)	4467.49 (4244.12 - 4690. 86)	[31]
One time cost of MH	2814.51 (2673.78-2955.24)	2814.51 (2673.78-2955.24)	[31]
One time cost of death	2321.82 (942.75 - 10849.16)	2321.82 (942.75 - 10849.16)	[31]
Cost discounting rate (%)	3.5 (0-5)	3.5 (0-5)	[25, 27]

Table 1: Input data for base-case and range for sensitivity analysis for both treatment opportunities. MI Myocardial Infarct, PE Pulmonary Embolism, MH Major Haemorrhage. SI-State Island, DJ Danbury Rajev – provided by Aalborg Hospital.

Prices illustrated in table 1 were estimated in accordance to PLO collective agreement for 2012 [30].

dkDRG was used to estimate transfer costs of one-time events of stroke, MI, PE and MH event. All incremental costs were corrected by half cycle, as these costs occur gradually during the cycle [26,35].

DATA INPUT, PROBABILITIES

In the analysis, rehabilitation cost is not included, why intentional assumption was made that the AF individual has no chance of returning to "well with AF on medication" state after an adverse outcome. In this lies another assumption that all these adverse events can be classified as "serious", which is also reflected in the utility weight for different health state events. It was assumed that all adverse events would result in a disability state. The AF patients were able to move between states, but would remain in any disabled state until absorbing state. For all adverse events, it was intentionally assumed that patients were continuing anticoagulant treatment, with adjustments. Intentionally, no assumptions were made linking the increased risk of adverse event in between, of the four types of side effects, as the literature search revealed no direct connections.

In the base case analysis, the annual rate of stroke was 1.67 % for warfarin and 1.05 % for dabigatran, as illustrated in table 1 [22,23]. For AF patients already in the diseased state due to an earlier stroke, an increase to 1.76 % for warfarin and 1.10 % for dabigatran was applied for the remaining years [37]. For MI, an annual risk of 0.67 % for warfarin and 0.83 % for dabigatran was estimated based on the number at risk in the RE-LY study [22,23]. In the case of previously MI, an increase to 0.74 % for warfarin and 0.91 for dabigatran % was used [38]. No age adjustment was made directly for the risk of MI, however this was incorporated in the utility score. In the RE-LY study, only a few participants in both treatment groups had a PE, giving a risk of 0.09 % for warfarin and 0.15 % for dabigatran [22,23]. A risk of second embolism was incorporated with an increased estimate to 0.10 % and 0.16 %, in accordance with the literature [39]. Major hemorrhagic event was assumed fixed, as this side effect was not connected with increase in age nor due to other severe side adverse outcome, but purely due to drug consumption [21,22,23].

DATA INPUT, OUTCOME

Given the focus on "value for money", QALY was chosen as an appropriate outcome in this study. An age specific reduction in QALY-weight by 0.026 per decade was inserted to reflect disutility associated with aging. This was done after recommendation of disutility assumptions in a Swedish study [18,40]. The utilities of the states are based on different studies, concerning the topic AF, and the disutility of QALY due to an adverse event. Starting utility was based on Sørensen et al. mean EQ-5D index score for Danish population in different decades of age [40]. For the cohort on warfarin, an adjustment by disutility due to AF diagnoses was incorporated from Gage et al., O´Brian et al., Shah et al., and Freeman et al. [14,41,42,43]. For disutility of the cohort on dabigatran, a former study of QALY for a previously direct thrombin inhibitor was applied from O´Brian et al., illustrated in table 1 [41]. For each adverse event, a disutility was subtracted from start utility in order to represent utility in each stated disabled state, results represented in table 1. By definition, dead from all causes had a utility score of 0. For one-way analysis discounting on 0.0 %, 3.5 % and 5.0 % was added, in accordance with NICE guidelines [25,29].

SENSITIVITY ANALYSIS

A one-way sensitivity analysis of all variables included was performed in order to test the robustness of the results to changes in the values of pertinent variables. A scenario analysis was chosen in order to analyse best-case worst-case for each variable, results represented by tornado diagram. Probabilities were derived from confidence intervals from the RE-LY trial, as well as from best evidence in literature. For probabilities that were not obtainable from literature, an assumption of ±5 % was changed. Utility was adjusted to best evidence literature concerning warfarin, and a subsequently identical interval was adjusted to dabigatran rates. For those not obtainable from literature, an assumption of ±20 % was made.

	Costs (GBP, £)		Quality Adjusted Life Years (QALY)		ICER (£ per QALY)
Time horizon	New	Standard	New	Standard	
Expected Value (1 year)	917.56	353.06	0.84	0.83	50969.98
Expected value (2 year)	1355.77	754.02	1.64	1.61	20210.92
Expected Value (5 years)	2444.39	1833.67	3.85	3.73	5042.30
Expected Value (26 years)	19845.51	8813.50	9.25	8.63	17652.44

Table 2: Incremental Cost Effectiveness Ratio (ICER) for 1st year, 2nd year, 5th year and lifetime perspective (26 years). New indicates treatment with dabigatran 150 mg x 2, while standard indicate warfarin 2.5 mg x 2. All calculations were made in TreeAge Pro Healthcare 2011 (TreeAge Software, Inc., Williamstown, Mass).

Costs for one time cost of events were adjusted in accordance with Danish case mix system, assuming different complications. Medicine costs were adjusted with a ±20 % assumption. Cost concerning INR value and follow up was adjusted in accordance with PLOs collective agreement from 2012, assuming that INR control was done at home for best-case and that double visits were the case for worst case scenario. A probabilistic sensitivity analysis (PSA), 2nd order Monte Carlo Simulation, was conducted using 10,000 hypothetical patients for warfarin and dabigatran treatment for a lifetime perspective. Each variable in the model was given a distribution based on range, shown in table 1. For costs, gamma distributions were applied. For incidence rates, a beta distribution was applied, as it can only assume the value from 0 to 1. For QALY estimates, a uniform distribution was applied [35]. All distributions were calculated by mean and standard deviation (SD) [26].

Cost effectiveness plane with 95 % ellipses and a cost effectiveness acceptability curve (CEAC) was applied to the incremental cost effectiveness ratios (ICER) distribution to identify which treatment option represents best value for money. A willingness to pay (WTP) thresholds of £ 20,000/QALY and £ 30,000/QALY gained for a lifetime perspective was used [29,44].

RESULTS

Table 1 features all direct costs per patient connected to the new and standard treatment option. Table 2 illustrates the ICER for the four different time horizons. Under the first year of anticoagulation therapy, an increase in health outcome as well as increase in health economic costs was observed for the new treatment option. The picture was identical at year two, five, and at a lifetime perspective (26 years). At the short-term perspective (first year), the ICER was not cost effective, as it exceeded the WTP thresholds of £ 20,000/QALY and £ 30,000/QALY. However, the picture changes for ICER calculation at year 2, 5 and 26, where ICER calculations were subjective to the WTP threshold of £ 30,000/QALY. For threshold of £ 20,000/QALY neither short term perspective (first year) or second year were cost effective.

Under base case conditions for a lifetime perspective, the total cost was £ 19845.51 for dabigatran and £ 8813.50 for warfarin, respectively. The quality-adjusted life expectancy was calculated to 9.25 QALY with dabigatran and 8.63 QALY with warfarin. The ICER comparing the two treatment options were £ 17652.44/QALY, placing it in the north-eastern corner (Q1) in a cost effectiveness plane, indicating an increase in cost corresponded by an increase in QALY.

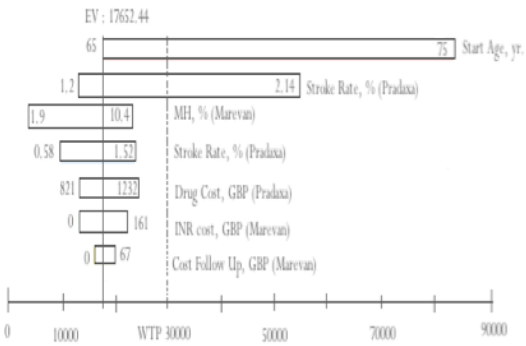

Figure 2: Sensitivity analysis; Tornado analysis for life time perspective. Bars indicate cost per additional quality adjusted life years (QALY) of dabigatran 150 mg twice daily compared with warfarin 2.5 mg twice daily, over a plausible range of variables. Bars are shown for seven variables, as those were the variables with the most impact on the incremental cost effectiveness ratio (ICER). Upper and lower limits of the seven variables evaluated in the analysis are indicated near the bars. Horizontal line indicates base case ICER (£ 17652.44/QALY), and the dotted line the threshold of £ 30,000/QALY. MH indicates Major Haemorrhage and INR international normalised ratio.

The one-way analyses, figure 2, showed that several pertinent variables influenced the cost effectiveness for a lifetime perspective. The incremental cost per QALY gained was mainly sensitive towards key parameters as stroke on dabigatran, patients' age, rate of major hemorrhagic events with both drugs, medical cost of dabigatran, and INR and follow up cost for warfarin. A range was found between £ 9400/QALY up to £ 80000/QALY, indicating that only starting age and stroke on dabigatran exceeded the WTP threshold of £30,000/QALY.

With a WTP threshold, of £ 30,000/QALY, dabigatran would be cost effective, except when expecting worst-case scenario for starting age and stroke rate for dabigatran. Also short term cost effectiveness was sensitive toward

changes in patients' age, mortality rate and INR costs, results not shown.

The result of the PSA for a lifetime perspective, is illustrated in the incremental cost-effectiveness scatter plot, figure 3. The scatter plot illustrates the cost effectiveness for 10,000 hypothetical AF patients, where all has higher cost as well as an increase in outcome (Q1), except 0.24 %, which was dominant (Q2).

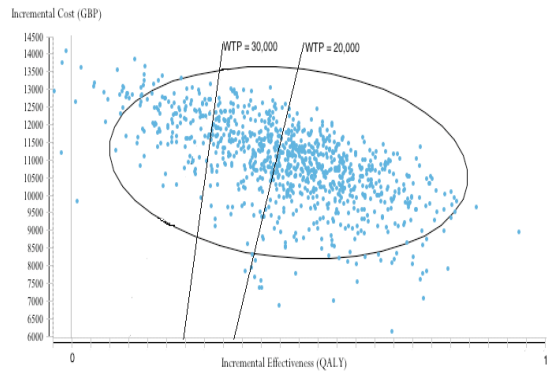

Figure 3: Estimated joint cost effectiveness density for AF treatment plotted on the cost effectiveness plane. The ellipse assumes 95 % of the estimated joint density on the cost effectiveness plane. Figure indicates a lifetime perspective of dabigatran versus marevan (10,000 iterations). Willingness to pay (WTP) threshold for £ 20,000/QALY and £ 30,000/QALy represented.

At a WTP of £ 20,000 per QALY gained to £ 30,000 per QALY gained the new oral anticoagulation drug, dabigatran, is 64 % cost effective compared with warfarin, see figure 3. Around 12 % was not cost effective. In the interval between WTP of £ 20,000/QALY and £ 30,000/QALY it is neither classified as cost effective nor classified as not being cost effective.

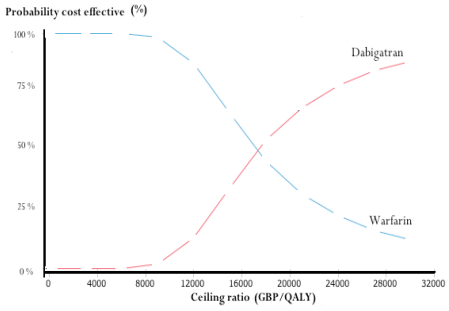

Figure 4: Cost Effectiveness Acceptability Curve (CEAC) for analysis for long term perspective (26 years).

The CEAC illustrates the probability of dabigatran being cost effectiveness at different WTP compared with current standard. Results show that with an increase in WTP, dabigatran seems to become a more cost effective option.

DISCUSSION

The ailments of AF patients, as those accounted for in this study, are associated with increased risk of mortality and morbidity, including high risk of stroke. Present anticoagulation therapy have shown to reduce the stroke risk by 64 %, but severe side effects, such as haemorrhagic bleeding, are associated, both leading to varying degrees of prolonged disability. Both the economic and personal burden of AF related adverse events are high, why new and safer treatment options are crucial.

In this study, a decision analysis was conducted in order to investigate the cost utility of dabigatran as a supplemental therapy to current treatment strategy for AF patients with $CHADS_2$ score of 1 or higher. The short term ICER (first year) was evaluated to £ 49091.52 per QALY. Although Danish threshold values concerning this area did not exist, threshold values in accordance with NICE recommendations were used, indicating that short term ICER exceeded the WTP, from a Danish health care perspective. Thus, it can be argued that extra cost does not exceed the effect outcome, which primarily is caused by the high drug-price of dabigatran. However this changes drastically from year one to year two and five, where the increase in QALY was seen as well as smaller increase in cost of dabigatran compared with warfarin.

At a lifetime perspective, it seems to be a cost effective alternative to current standard treatment to substitute warfarin with dabigatran. The increase in cost during a lifetime perspective was compensated by an increase in effect outcome. If this is true in accordance with the model in this study, the higher costs of medicine do not affect the overall lifetime economic advances. This study indicates if patients survive the first year, the drug seems to be cost effective approach for prevention of stroke. Therefore, it would be recommended to investigate long-term consequences of the newer drug in real life settings.

The one-way sensitivity analysis revealed that key parameters as stroke rate, patients' age,

rate of MH and cost connected to drug, were of great importance for ICER calculation. As the study was primarily based on the RE-LY study, which claimed to reduce the stroke rate as well as MH events, it leads to questioning if we can rely on the RE-LY study to conclude if this is a cost effective substitute to warfarin in Danish settings.

LIMITATIONS

Several caveats apply to results of this decision analysis. Treatment in practice may not be as effective as reported by the RE-LY study, as randomised trials generally enroll healthier patients than those found in real life settings. Thus, high levels of adherence and greater monitoring and drug adjustment of patients must be expected. Further, all incidence rates extracted from the RE-LY study represent a mean from several different countries with different cultures of treatment. In Sweden, a cost effectiveness analysis was made indicating that with sufficient monitoring of warfarin treatment (corresponding to stable INR level), warfarin was the most effective treatment option over a lifetime perspective [18].

Assumptions made as a part of this analysis were extremely conservative and beneficial for the new drug. However, there may be a change in costs if patients were able to transfer to a post-adverse event state, as it is known that only about half of strokes are classified as minor strokes, wherefore patients are not equally disabled as for major strokes [37]. This also translates to the other states events. Meanwhile, it must be remembered that patients never return to fully well after an adverse event, they will still be disabled in some kind of way. This is also influenced by different strategies of physiotherapy as well as ergo therapy (rehabilitation). Additionally, in the event of stroke, depending on time of diagnosis, treatment options, such as intravenous thrombolytic, may also have an effect on recovery and quality of life estimates [45].

As majority of this analysis was based on the RE-LY study, the rates were based on non-Danish settings, which may have a large impact on accuracy of ICER calculations. It is suggested for the improvement of reliability and validity that an investigation at Danish hospitals should be conducted in order to convert incidence rates for the difference between dabigatran and warfarin in Denmark.

The RE-LY study was conducted on a short-term study investigation of two years. When calculation of these events for life-time it may be expected that incidence rates increase, as well as further age-depend diseases will appear. This weakens the strength of this study, wherefore a long-term investigation is recommended.

RE-LY – A GREAT TOOL ?

The RE-LY study was a non-inferior study, whereby dabigatran was not proven to be inferior to warfarin, and thereby not possible to directly substitute. All of the above begs the question why dabigatran was accepted by the Danish health authorities, as the study, despite being the largest ever preformed in its field, was not proven inferior to currently treatment options. Further RE-LY does not use blinding for the warfarin group, why a high-risk bias may be undetected. This was amply demonstrated by ximelagatran, an earlier thrombin inhibitor, which, similarly to dabigatran, indicated that stroke, was reduced. However, follow up study proved this to be wrong, and instead the drug showed greater number of strokes [46].

Even though it was chosen to use data from the RE-LY study, a critical approach was taken before entering data. The mortality rate was adjusted to Danish settings, as the mortality rate in the RE-LY study had a rate corresponding to AF patients in Denmark receive no anticoagulant treatment [33]. In NICE, guidelines have been made, as for only applying dabigatran for those patients whom are not responding well to warfarin treatment [34].

During literature search, it was found that primarily all data connected to the dabigatran topic was directly and indirectly connected to the producent, and that all was based purely on the RE-LY study, and thus lack of transparency was a concern. NICE guidelines concerning dabigatran, indicate several concerns of data reported in cost effectiveness analysis. Most importantly, the utility scores used had no transparency and no health related benefits were identified that were not in these economic models [34].

CONCLUSION

In conclusion, this study suggests that, with a lifetime perspective the new anticoagulation drug dabigatran might be a cost effective approach for stroke prevention for AF patients with $CHADS_2$ score of 1 or above, when compared to the standard. However, these results must be taken with caution, as conservative approach in the favour of dabigatran was taken and the reliability of the RE-LY study is questionable in Danish settings. Furthermore, results were not based on purely Danish studies, hence why it must be expected that some variation can be discovered.

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