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# Cost-Effectiveness of Dabigatran Exilate in Treatment of Atrial Fibrillation

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**Abstract**

**Background:** Dabigatran exilate has emerged as a highly effective tool in treating atrial fibrillation, AF). Its relative convenience in terms of cost and overall utility with respect to other anti-coagulants, however, has not been explored in much detail yet.

**Methods and Results:** We run a Markovian disease simulation model based on a cohort of 1000 randomly generated patients which were sub-grouped by average risk of hemorrhage and average risk of stroke to compare treatments with Aspirin, Warfarin and Dabigatran. Quality-adjusted life-year, QALYs) for the patients were projected over up to 30 years with mortality statistics database and properly adjusted after every 5-year survival from the starting date. If managed within the prescribed range, Warfarin offers the highest outcome in terms of QALYs: 7.93 versus 7.61 for the Aspirin treatment and 7.57 for highest dose treatment with Dabigatran. Dabigatran outperformed the other treatments in patients at high risk of major stroke, provided Warfarin was not managed optimally. The incremental cost-effectiveness ratio for Dabigatran versus sub-optimally managed Warfarin was €7,759.48/QALY meaning that every year in perfect health earned with Dabigatran cost less than €8,000 more than the alternative treatment with Warfarin.

**Conclusions:** The therapy with high-dose Dabigatran proved the most clinically safe solution for patients at high risk of stroke unless Warfarin therapy was excellent.

## Introduction

The paper aims to identify a criterion to determine the relative convenience, in terms of cost and overall utility, of several oral anticoagulants therapies in treating patients affected by atrial fibrillation.

The research stems from the need of further exploring and comparing the efficacy and convenience of Dabigatran Exilate vis-à-vis other anti-coagulant drugs in treating atrial fibrillation (AF) and the belief that stroke prevention through the adoption of a safe and effective antithrombotic therapy is a primary objective to be pursued without delay.

## Clinical Perspective

The Atrial Fibrillation, AF, is the most common and wide-spread cardiac arrhythmia.

According to several studies, the prevalence of AF in the general population is of little less than 1%, 0.90% in Europe[1] and 0.95% in USA.[2] However, these numbers only account for the diagnosed cases and may therefore be significantly underestimated since silent, and/or asymptomatic AF represents a big slice of the entire affected population, 25% in Olmsted County study.

According to the latest data people affected by AF are almost 3 million in USA and 5 million in Europe and but if we adjust for the silent cases these numbers would rise respectively to 3.75 million and 6.25 million.[3]

The number of individuals diagnosed with conditions considered risk factors for AF, such as ischemic heart disease, heart failure, obesity, and diabetes has been increasing in recent years and it is widespread belief that this pattern will continue in the future.

The fight against atrial fibrillation is thus a major challenge for public health systems around the world.

The increase in the incidence and prevalence of AF with the general aging of the population implies a considerable cost to the public finances, which is constantly growing. In fact, despite the improvements in the health sector, the prognosis of the complications of AF, primarily stroke has not improved much, while, aging population playing its part, mortality and hospitalizations have steadily increased insomuch as currently, in the European Union, the overall burden on society related to AF amounts to €13.5 billion, approximately $15.7 billion.

As a consequence, the prevention of stroke through the adoption of a safe and effective antithrombotic therapy is a primary objective to be pursued without delay.

**Disclosures:**
None.

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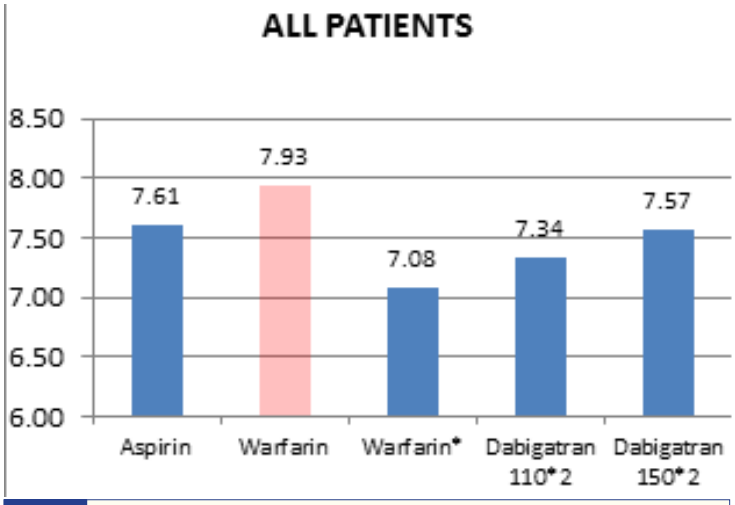


**Figure 1:** Average QALYs lived by all patients

## Methods

The work was carried out on a virtual sample of patients with atrial fibrillation and with an average age of 75 years.

On the basis of the results from Randomized RE-LY trial, we developed a decision-analysis model to compare the cost and quality-adjusted survival granted by the antithrombotic therapies with Aspirin, Warfarin and Dabigatran, either 2*110mg/die and 2*150mg/die doses for each category of patients.

To run our cost-efficiency analysis we utilize a Markovian model so that the creation of the follow-up is guided by the probabilities related to the case records of atrial fibrillation only and does not suffer interferences due to clinical events of other nature.

We generated our 1,000 patients sample by assigning to each combined age and gender of the patient a probability of being picked up consistent with the data of the actuarial life table of the US Social Security Administration[4] and we do so implementing the Microsoft Excel's RANDOM() function.

We set the Dabigatran treatment cost at 6.00€/day, based on an average of selling prices found online for an overall cost of €2,190/yr.

Wanting to determine which is the most cost-effective treatment for each category of patients, and not in overall terms, we group the hypothetical cohort based on the average risk of hemorrhage and the average risk of stroke using respectively the HEMORR2AGES and the CHADS2 score.

HEMORR2AGES is the acronym of a 11-item scoring system, developed by Gage BF, Yan Y Milligan PE, et al. for estimating the risk of major bleeding in patients based on:[5]

- Hepatic or renal disease
- Ethanol abuse
- Malignancy
- Older age, ≥75
- Reduced platelet count or function
- Rebleeding risk, i.e.: prior bleed
- Anemia
- Genetic factors, CYP2C9 variant
- Excessive fall risk
- Stroke

The presence of every risk factor contributes 1 point to the final score, except prior bleeding which is assigned a weight of 2 which will be between 0 and 12.

CHADS2 is a score based on several clinical parameters built to estimate the likelihood of stroke in patients affected by non-rheumatic atrial fibrillation, AF. It is based on the following conditions[6]:

- Congestive heart failure
- Hypertension: blood pressure consistently above 140/90 mmHg
- Age ≥75 years
- Diabetes mellitus
- Prior stroke or Transient Ischemic Attack, TIA

Again, every condition contributes 1 point, with the exception of prior stroke or TIA which is assigned a weight of 2 to the final score.

To accommodate the natural distribution of patients depending on their CHADS2 and HEMORR2AGES scores, we utilize three sub-groups for each score, tables 6 and 7:

Once we have randomly – but consistently – generated our "virtual" patient we simulate how his follow-up will be. We extended the simulation of the follow-up period up to 30 years, convinced by the fact that the number of patients that would outlive such period, taken into account that the average age of the sample is around 75, will be few enough not to be statistically relevant – nor influential on the calculations as well.

Each follow-up year is associated with an utility level going from 0 to 1, where 1 represents a perfect state of health and 0 is given to death. The utility values associated with each adverse event were assigned according to the following table[7] and were determined through a questionnaire by the same patients observed during the RE-LY trial:

Even if some health states may be considered worse than death when they cause extreme pain and discomfort, thus having negative scores, we here decided to put a floor at 0.

Cardiovascular events, however, do not account themselves for all reduction in the yearly life utility of patients. Mortality rate was introduced in the calculation of patients' QALYs and continuously adjusted, with a frequency of five years to take into account the increased likelihood of the patients of dying as they age. Mortality rates were derived manipulating the data found in CDC/NCHS, National Vital Statistics System database[8] and suitably linking them to a function which assigned a value of 1 if the observed

**Table 1:** Incidence of major bleeding according to HEMORR2AGES score

| Risk Score | Incidence of Major Bleeding (Bleeds per 100 patient-yrs) | 95% CI |
|---|---|---|
| 0 | 1.9 | (0.6-4.4) |
| 1 | 2.5 | (1.3-4.3) |
| 2 | 5.3 | (3.4-8.1) |
| 3 | 8.4 | (4.9-13.6) |
| 4 | 10.4 | (5.1-18.9) |
| ≥5 | 12.3 | (5.8-23.1) |

**Table 2:** Incidence of stroke according to CHADS2 score

| Risk Score | Incidence of Stroke(%) | 95% CI |
|---|---|---|
| 0 | 1.9 | (1.2-3.0) |
| 1 | 2.8 | (2.0-3.8) |
| 2 | 4.0 | (3.1-5.1) |
| 3 | 5.9 | (4.6-7.3) |
| 4 | 8.5 | (6.3-1.1) |
| 5 | 12.5 | (8.2-17.5) |
| 6 | 18.2 | (10.5-27.4) |

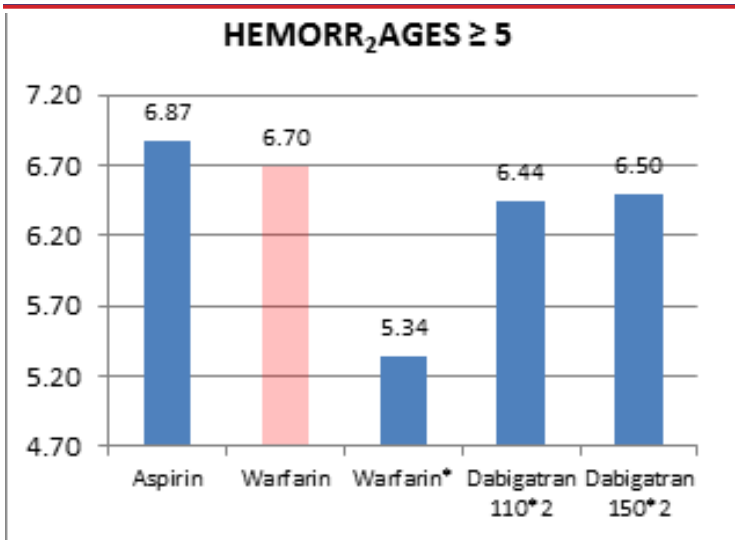


**Figure 2:** Average QALYs lived by patients at high risk of hemorrhage

patient survived in that year or a value of 0 if that patient died with probabilities in accordance with the mortality table values.

Once a complete 30-year follow-up is generated for each patient we can compute the average QALYs for the different treatments. We can thus compute the overall average QALYs and the average QALYs for patients with high CHADS2 and HEMORR2AGES scores to compare the differences in efficacy of the four therapies according to their reported scores.

Is crucial to notice that, unlike patients treated with Aspirin and Dabigatran, patients that were administered Warfarin had their overall utility also affected by the time on therapeutic range, TTR. TTR is the percentage of time the patients treated with vitamin K antagonists manage to stay inside their prescribed INR.

This is of paramount importance because, as it was proven by Stuart J. Connolly et al. in a study published on "Circulation – the Journal of American Heart Association",[9] little benefit exists over antiplatelet therapy if the TTR of the treated patients falls below a determined threshold that varies among countries and centers but can be estimated between 58% and 65% and is achieved by just two thirds of the sample.

As emerged from this study for patients at centers with TTRs above the median, ≥ 65%, oral anticoagulant, OAC reduced vascular events more than 2-fold, RR, 2.14; 95% CI, 1.61 to 2.85; P-value < 0.0001 while for patients at centers with mean TTRs below the median, < 65%, no statistical significant reduction in events occurred with OAC, relative risk, 0.93; 95% CI, 0.70 to 1.24; P-value= 0.61.

As a consequence, before putting the averages at comparison and re-iterate the simulation to see if there is any consistent and statistically relevant difference among the therapies, we must adjust the utility derived by the treatment with Warfarin by taking into account for the incremental "disutility" caused by not being in range, the target range defined by the guidelines in force now is an INR of 2 to 3.[10]

[U]Wadjusted = [U]W ∈ range * p(range) + [U]Wnot ∈ rang * p(not ∈ range)

Or

[U]Wadjusted = [U]W∈range - ([U]W ∈ range - [U]Wnot ∈ range) * p(not ∈ range)

where

[U]Wnot ∈ range = [U]noAF - ([U]noAF - [U]W ∈ range)*RR

To find "\ left\ \[U\ right\ \]\ \ no\ AF" we run another simulation where the yearly utility of our hypothetical cohort of patients is only affected by the mortality rate values derived from our previous table.[11]

After having run 20 simulations we decide to use 10 as the average QALYs lived by the patients not affected by AF, mean: 10.035, standard deviation: 0.30 and to use such number as our base-case.

For what concerns the determination of RR we compute the proportion of patients who experienced an adverse event in both the first and the second two quartiles, so they are respectively divided into "not in range" and "in range" and divide the former by the latter.

(RR=(% of"not\ in\ range\ "patients,adverse event)/(% of"in\ range\ "patients,adverseevent))

We decide to base our calculations on the values including stroke, myocardial infarction, systemic embolism, vascular death and major hemorrhage due to their greater comprehensiveness.

Last but not least, we must remember that the implementation of a Markov model implies that the outcomes are modeled as a transition from an health state to another, i.e. "well" in year 4 to "Myocardial Infarction" in year 5 and that we are assuming the transition probabilities remain constant notwithstanding the emergence of an adverse event or an occurred transition.

## Results

After having run our simulation for 20 times we calculate the average QALYs lived under each therapy.

As expected, if we take into consideration the whole cohort of patients we see that Warfarin, if well managed within the prescribed range, offers the highest outcome in terms of QALYs: 7.93, followed by Aspirin,7.61 QALYs and the two treatments with Dabigatran,7.57 for the 2*150mg/die dose and 7.34 for the Dabigatran 2*110mg/die dose.

The QALYs obtained with Warfarin, however, drop dramatically to 7.08 if they are adjusted by the portion of patients outside therapeutic range for more than 35% of the time, making Warfarin

**Table 3:** patients distribution according to CHADS2 score

| | |
|---|---|
| CHADS2 0-1 | 31,90% |
| CHADS2 2 | 35,60% |
| CHADS2 3-6 | 32,50% |

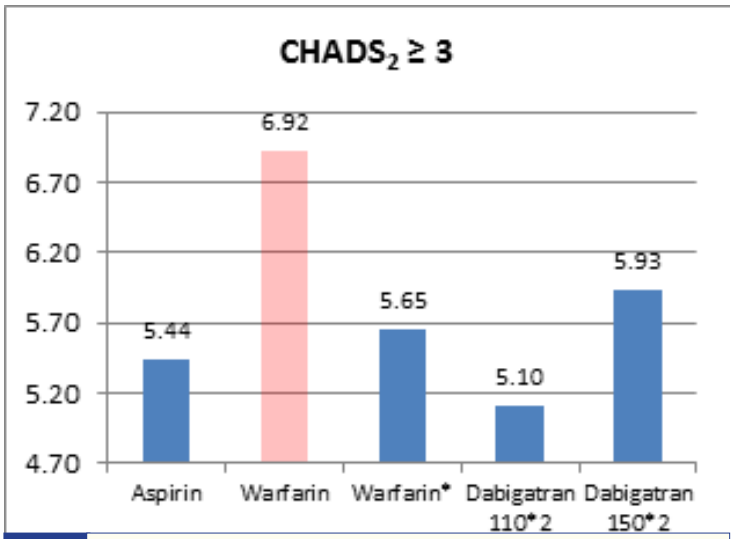


**Figure 3:** Average QALYs lived by patients at high risk of hemorrhage

the least effective therapy.

If we now consider the patients at high risk of major bleeding events,HEMORR2AGES score ≥ 5, Aspirin proves to be the best choice at 6.87 QALYs, with 0.17 QALYs over Warfarin,TTR≥65%, 0.37 QALYs over Dabigatran 2*150mg/die,6.50 QALYs, 0.43 QALYs over Dabigatran 2*110mg/die,6.44 QALYs and 1.53 QALYs over the adjusted Warfarin, 5.34 QALYs.

Dabigatran 2*150mg/die is instead the best alternative for patients at high risk of major stroke(CHADS2 score ≥ 3) with an average of 5.93 QALYS. The QALYs of the other therapies were: 5.44 for the Aspirin, 6.92 and 5.56 for Warfarin,TTR≥65% and TTR≤65% respectively and 5.10 for Dabigatran 2*110mg/die.

To sum up, Warfarin would be the best choice overall and especially for patients with high risk of stroke, but only provided that the therapy is managed well enough to maintain the INR within the prescribed range for at least 65% of the treatment time. Nonetheless, even if most of the centers in almost all advanced countries succeed in keeping within range the vast majority of patients with AF, there are still many that are still not able to reach a TTR of 60%, among them, Belgium(9).

The therapy with Dabigatran, in its 2*150mg/die dosage, provides instead the most clinically safe solution for patients at high risk of stroke,CHADS2 score ≥ 3 unless INR control was excellent (i.e. top quartile).

**Cost effectiveness in detail**

Applying the Incremental Cost-Effectiveness Ratio, ICER to Dabigatran 150mg twice daily and Warfarin using the following data:

€2.5 per tablet for Dabigatran 150mg

€1.5 per month, tablets + €450 per year, INR monitoring for Warfarin.[12]

We get an ICER of €7,759.48/QALY, meaning that every year in perfect health earned with Dabigatran cost less than €8,000 more than the alternative treatment with Warfarin.

## Discussion

On the basis of what has been argued so far and the results of the complex statistical work just described, the clinical fields in which the analyzed oral anticoagulants optimally perform their therapeutic action in the treatment of atrial fibrillation have been identified and their relative cost effectiveness has been evaluated.

As a consequence the following considerations can be made:

For a patient with an average risk of major hemorrhage, (≈3%/y) the most cost-effective therapy depended on stroke risk.

For patients with the lowest stroke rate (CHADS2 stroke score of 0) only Aspirin was cost-effective.

For patients with a moderate stroke rate (CHADS2 score of 1 or 2) warfarin was cost-effective unless the risk of hemorrhage was high or quality of international normalized ratio control was poor, time in the therapeutic range <57.1%.

For patients with a high stroke risk (CHADS2 stroke score ≥3), Dabigatran 150 mg, twice daily was cost-effective unless International Normalized Ratio control was excellent (i.e. time in the therapeutic range >72.6%).

**Table 4:** patients distribution according to HEMORR2AGES score

| | |
|---|---|
| HEMORR2AGES 0-1 | 40,3% |
| HEMORR2AGES 2-4 | 39,2% |
| HEMORR2AGES 5-12 | 20,5% |

**Table 5:** Utility values of adverse clinical events according to RE-LY trial questionnaire

| Clinical Event | Base case | Range |
|---|---|---|
| Neurological event with residua | | |
| Mild | 0.75 | 0–1.0 |
| Moderate to severe | 0.39 | 0–1.0 |
| Recurrent | 0.12 | 0–0.5 |
| Temporary states | | |
| Major bleeding, other than ICH | 0.8 | 0.5–0.99 |
| Minor bleeding | 0.8 | 0.5–0.99 |
| Initiating warfarin therapy | 0.98 | 0.9–1.0 |
| Myocardial infarction | 0.87 | 0.8–0.9 |

Neither Dabigatran 110 mg nor dual therapy (Aspirin and Clopidogrel) was cost-effective.

Is a clear need that all centers in which AF treatment takes place should attempt to achieve the highest possible TTR although this is challenging and the existing economic conditions of the health administration may oppose it.

In any case, in the light of current data, it is essential that clinics, hospitals, and in general any medical center, assess the TTR achieved by its patients and even if the values of this parameter can vary greatly from subject to subject, it is necessary to set a minimum target TTR of 60-65%.

We would thus encourage the staff of medical facilities – that for biological, systematic, economic or other reasons cannot achieve proper TTR level – to prefer the use of Dabigatran to Warfarin or Aspirin in patients with atrial fibrillation.

## Conclusion

Our work are based on modeling and a set of prior data, it may thus be possible that the results of this simulation may not be applicable to settings, different to the one that was utilized.

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