Original Research

Economic Evaluation of Dabigatran Etexilate in the Management of Atrial Fibrillation in Greece

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Introduction: The objective of the present study was to evaluate, from an economic perspective, dabigatran etexilate in comparison to existing pharmaceutical therapeutic options available for the protection of moderate-to-high risk patients with non-valvular atrial fibrillation from cardioembolic risk.

Methods: An existing Markov model was adapted to the Greek setting to reflect the natural course of the disease and the management of patients with different therapies. The model predicts health and economic outcomes and the implications for the social security system during the course of a patient's lifetime. The data for the population of the model were derived from the international literature and local economic databases.

Results: The incremental cost per quality-adjusted life year (QALY) of dabigatran 150 mg twice daily relative to the other therapies varied from €5547 to €11,762 and that of dabigatran 110 mg twice daily from €7398 to €16,437. The incremental cost per QALY of dabigatran 150 mg relative to aspirin, the least costly option, was €11,762 and relative to warfarin and acenocoumarol, the local standards of care, it was €11,400 and €11,224 respectively, well below the local thresholds of acceptance.

Conclusion: Dabigatran etexilate may represent a cost-effective option for the prevention of thromboembolic events in AF patients at moderate-to-high risk of stroke or systemic embolism.

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Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting about 1-2% of the general population. Its prevalence is age-dependent and increases from <0.5% in those aged 40-50 years to 5-15% in those aged 80 years or over; hence, given the prevailing demographic trends, the number of sufferers is expected to increase significantly in the near future.[1-8] This means that AF represents a significant public health problem, as it has been associated with increased rates of stroke, systemic embolism, heart failure and left ventricular dysfunction, which in turn result in reduced exercise capacity and quality of life, and higher death rates.[7,9-12] Moreover, because of its associated morbidity and mortality, AF also imposes a significant demand on health care services and thus represents a great contribution to the national economic burden.[13-24] In particular, given the demographic changes that have occurred during the last decades in Greece and the high prevalence of hypertension, two of the most important risk factors for AF, this arrhythmia is of great significance for the Greek population.[25] In view of the above, it is important to manage AF patients effectively and efficiently.[26]

The main objective in the care of AF patients is simultaneously to reduce symptoms and to prevent complications. With regard to the latter, a cornerstone in the management of patients is antithrombotic therapy, which is used in order to prevent serious events such as stroke and embolism. International guidelines issued by the European Society of Cardiology[25] and local recommendations[27,28] provide guidance on how to manage patients based on

their risk status, the latter being defined in terms of their $CHADS_2$ (cardiac failure, hypertension, age, diabetes, $stroke_2$) score. According to local recommendations, for patients with one risk factor acetylsalicylic acid or anticoagulation therapy may be used, with a preference for the latter, and for those with two or more risk factors anticoagulation therapy with vitamin K antagonists (VKA) such as warfarin and acenocoumarol is recommended, with an international normalised ratio (INR) target of 2.0 to 3.0, and assessment every 15 to 30 days for individualised therapy dose management.[27] However, because of their pharmacokinetic profiles and the multiple food-to-drug and drug-to-drug interactions, the above therapies require regular assessments and dose adjustments in order to attain the desired effects, and this is not always possible in real-life practice. Owing to the above drawbacks, dual antiplatelet therapy has been used extensively by physicians, despite the fact that recent trials and registries, as well as the latest ESC guidelines, stress the fact that "aspirin plus clopidogrel therapy could perhaps be considered as an interim measure where VKA therapy is unsuitable, but not as an alternative to VKA in patients at high bleeding risk."[27]

From the above, it is clear that there is a need for a new, more efficacious, safe and convenient treatment for stroke and embolism prevention in AF patients. Dabigatran etexilate, an oral direct thrombin inhibitor, represents a new anticoagulant option for use in this group of patients. The Randomized Evaluation of Long-term anticoagulant therapY (RE-LY) clinical trial evaluated this therapy, relative to adjusted-dose warfarin, in the prevention of stroke and systemic embolism amongst non-valvular AF patients.[29] It was shown that, at a dose of 150 mg twice daily, dabigatran is associated with lower rates of stroke and systemic embolism and similar rates of major haemorrhagic bleeding compared to vitamin K antagonists, whilst at a dose of 110 mg twice daily, dabigatran is associated with lower rates of haemorrhagic bleeding and comparable rates of ischaemic strokes and systemic embolism; it can therefore represent a viable alternative when it becomes available locally.[27]

Health resources are scare and they should be used wisely. Demographic and technological trends are pushing budgets upwards, and for this reason it is important to find ways that can aid decision makers to direct resources to the most efficient therapies. This is even more important in the context of the present global financial crisis and the pressures on public budgets. Especially for Greece, it is paramount to improve the efficiency of decision making and resource allocation, as in the past three years the country has received a loan in the context of an international rescue package and in return has been asked by its creditors (the International Monetary Fund, the European Commission and the European Central Bank) to implement rigorous reforms. Amongst other measures, they aim at cutting pharmaceutical spending by 50%, in order to bring it in line with other EU countries and to maintain public health care spending below 6% of the Gross National Product. In this context there is competition for resources and an immense need to invest them properly. The question may be raised as to whether money should be spent on new, innovative, but also more expensive therapies. To guide efficient resource allocation, an economic evaluation was undertaken in order to assess the therapeutic alternatives available for thrombophylaxis in the management of AF patients in Greece and the present paper presents the results of this economic analysis.

Methods

Model design

The objective of the present study was to compare from a cost-effectiveness perspective dabigatran etexilate (150 mg or 110 mg twice daily) relative to other locally available therapies, in patients with non-valvular AF at moderate-to-high risk of stroke or embolism, eligible for anticoagulation treatment. According to local guidelines the main option is adjusted-dose warfarin (up to 5 mg per day), with a target therapeutic international normalised ratio (INR) of 2.0 to 3.0, but in clinical practice acenocoumarol (up to 2.5 mg per day) represents the standard of care. Also, acetylsalicylic acid monotherapy (162.5 mg per day) and acetylsalicylic acid plus clopidogrel (75 mg per day) are often used. Hence all the above therapies were considered.

The analysis was based on the local adaptation of a previously published Markov model, which was designed to reflect the natural progression of AF patients through different health states, during the course of three-month cycles, up to death.[30,31] The model concept is depicted in simplified form in Figure 1 and its detailed structure is described in full elsewhere.[30,31] The clinical events considered include primary and recurrent ischaemic stroke, haemorrhagic stroke, transient ischaemic attack, systemic embolism, acute myocardial infarction, intracranial haemorrhage, extracra-

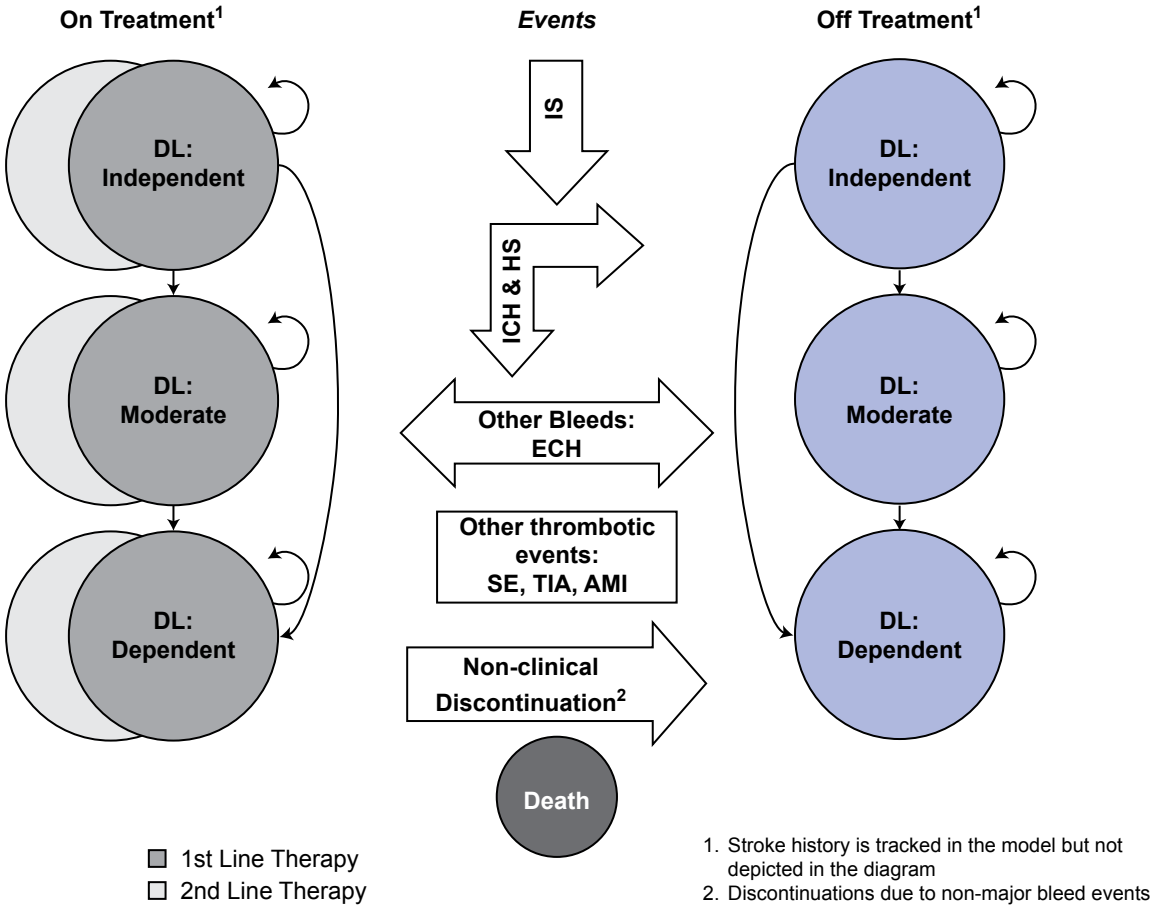

Figure 1. Schematic of the Markov model. From reference 41. Reproduced with permission. DL – disability level; IS – ischaemic stroke; ICH – intracranial haemorrhage; HS – haemorrhagic stroke; ECH – extracranial haemorrhage; SE – systemic embolism; TIA – transient ischaemic attack; AMI – acute myocardial infarction.

nial haemorrhage and death. The model is driven by the likelihood of occurrence of the above events and quantifies their impact on treatment status, patient survival, dependency status, quality of life, resource utilisation and total therapy cost.

A cohort of 10,000 AF patients enters the model and starts in each one of the treatments under evaluation. In each subsequent three-month model cycle during their life span, patients can then either remain without any event or experience the abovementioned clinical events and eventually death. Patients can also experience minor bleeds during any model cycle, regardless of whether they experience a major clinical event in the same cycle. Major events, such as stroke, have an impact on patient disability level (independent, moderately dependent or totally dependent), treatment status (on treatment, switching treatment, temporary or permanent discontinuation of treatment), or result in death. Patients can also switch or discontinue treatment permanently for reasons not related to a clinical event. Notably, over time, patients can also die from other causes based on age- and gender-adjusted all-cause mortality data. Patients who are on treatment are assumed to be subject to its benefits on a constant basis over time, whilst those who are off therapy are assumed to be unprotected. In all cases but acetylsalicylic acid-based therapy, patients are switched to acetylsalicylic acid monotherapy in the case of a discontinuation and its event rates and cost are assumed thereafter.

Population

The baseline patient population for which results were estimated is that of the Randomized evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial.[29] The sample consisted of non-valvular AF patients, primarily at moderate-to-high risk of stroke or embolism, and eli-

gible for anticoagulation treatment. The main characteristics of the sample were: male 64%, mean age 71 years, systolic blood pressure 131 mmHg, diastolic blood pressure 77 mmHg, previous stroke or transient ischaemic attack 20%, prior myocardial infarction 17%, diabetes 23%, heart failure 32%, and hypertension 79%.[29] Local studies have shown that the local AF population is similar to the one recruited in RE-LY.[25,32]

Perspective

The health care system in Greece is complex and under reform. The provision of services is undertaken mainly by a National Health Service (NHS), which is funded by direct Government subsidies and Social Security Sickness Funds. The former mainly covers the salaries of the personnel and the later the remaining operating costs. The Sickness Funds were recently merged into a single one that covers most of the population. This fund provides for all outpatient treatment and the non-salary cost of inpatient care, through recently introduced local diagnosis-related group-type tariffs. These tariffs are also used when patients are treated in private hospitals. Hence, the perspective of the economic evaluation was that of the public third-party-payer. In this light, only health care costs reimbursed by the payer were considered in the analysis and any other cost, such as the cost related to the central Government budget or patient co-payments, was not considered. The horizon of the analysis was set at the lifetime of patients and all outcomes were discounted at 3.5%. A half-cycle correction was used. In the extrapolation period beyond the RE-LY trial, benefits were assumed as long as patients were on therapy, i.e. anticoagulated.

Effectiveness and health outcomes

In the model, adjusted-dose warfarin and its event rates from the RE-LY trial[29] represent the baseline risks, as presented in Table 1. Relative risks were then applied to estimate the event rates of the remaining therapies. The relative risks of the two dabigatran doses also came from the aforementioned trial.[29] A meta-analysis was used to model the relative risk of no treatment and acetylsalicylic acid-based therapy.[31,33] Warfarin and acenocoumarol share a similar chemical structure and bind to the same receptor binding site. Thus, acenocoumarol is frequently used instead of warfarin in some European countries including Greece, where it represents the standard of care. Based on a literature search and expert advice, acenocoumarol and warfarin do not appear to have any statistically significant differences in terms of the total number of patients within the therapeutic range, and their efficacy and use in clinical practice.[34-37] Hence, for the purposes of our analysis, it was assumed that acenocoumarol and warfarin have identical efficacy and safety, and that they differ only in terms of price. This assumption is also justified as the anticoagulation is targeted at the same INR range of 2-3. After ischaemic and haemorrhagic stroke and intracranial haemorrhage, patients may die or change their dependency status, as presented in Table 2, based on the original modelling approach employed. Finally, based on literature data, it was assumed that 90-day mortality is 0.06% after systemic embolism, 1.11% after acute myocardial infarction, higher than 7% after myocardial infarction, and 0.03% after extracranial haemorrhage, and that the relative risk of death in moderate and totally dependent patients was 2.0.[31,38-40]

Quality of life

Utility values for each functional status are described in detail elsewhere.[31] The baseline value was 0.81, and there are different values according to impairment status as follows: independent with stroke history (0.650), moderately dependent (0.460), and totally dependent (0.300). Each event is associated with marginal disutilities, as follows: ischaemic stroke (0.139), haemorrhagic stroke (0.120), transient ischaemic attack (0.103), systemic embolism (0.120), acute myocardial infarction (0.125), intracranial haemorrhage (0.181), extracranial haemorrhage (0.181) and minor bleed (0.004).[31]

Discontinuation and switching

Patients may discontinue therapy following serious events and gastrointestinal symptoms. In the model it was assumed that all patients stop their treatment after a major intracranial haemorrhage or haemorrhagic stroke event, while half of them stop permanently after extracranial haemorrhage and the other half for 3 months. For warfarin and dabigatran, rates were estimated from the RE-LY trial, whereas for the remaining therapies data were drawn from the literature.[31]

Treatment cost

The cost inputs used in the model are depicted in Table 3. The cost of medications was estimated by combining data on their daily dose and the corresponding drug prices, obtained from the latest (January 2012)

Table 1. Annual event rates and relative risks of clinical events for each therapy.[30,31,33] In the probabilistic analysis baseline risks have beta distributions and relative risks log-normal.

Event	Rate/relative risk	95%LCI	95%UCI
Ischaemic stroke:			
Warfarin risk ($CHADS_2$ 0)	0.62		
Warfarin risk ($CHADS_2$ 1)	0.77		
Warfarin risk ($CHADS_2$ 2)	1.01		
Warfarin risk ($CHADS_2$ 3)	1.75		
Warfarin risk ($CHADS_2$ 4)	1.75		
Warfarin risk ($CHADS_2$ 5)	3.34		
Warfarin risk ($CHADS_2$ 6)	3.34		
No treatment relative risk	3.47	2.33	5.66
Aspirin/clopidogrel relative risk	1.95	0.79	3.46
Dabigatran 150 mg bid relative risk	0.76	0.59	0.97
Dabigatran 110 mg bid relative risk	1.10	0.88	1.38
Acetylsalicylic acid alone relative risk	1.68	1.00	3.02
Systemic embolism:			
Warfarin risk	0.18		
No treatment relative risk	4.31	1.69	10.03
Aspirin/clopidogrel relative risk	3.58	1.36	10.64
Dabigatran 150 mg bid relative risk	0.61	0.30	1.21
Dabigatran 110 mg bid relative risk	0.71	0.37	1.38
Acetylsalicylic acid alone relative risk	1.71	0.66	4.43
Transient ischemic attack:			
Warfarin risk	0.84		
No treatment relative risk	1.18	0.59	2.30
Aspirin/clopidogrel relative risk	1.56	0.91	2.65
Dabigatran 150 mg bid relative risk	0.86	0.65	1.15
Dabigatran 110 mg bid relative risk	0.74	0.55	1.00
Acetylsalicylic acid alone relative risk	1.56	0.91	2.65
Intracranial haemorrhage:			
Warfarin risk	0.39		
No treatment relative risk	0.33		
Aspirin/clopidogrel relative risk	0.52	0.18	1.34
Dabigatran 150 mg bid relative risk	0.55	0.34	0.89
Dabigatran 110 mg bid relative risk	0.32	0.18	0.58
Acetylsalicylic acid alone relative risk	0.55	0.20	1.41
Age adjustment (>=80)	1.80	1.10	3.10
Haemorrhagic stroke:			
Warfarin risk	0.38		
No treatment relative risk	0.33		
Aspirin/clopidogrel relative risk	0.65	0.04	5.63
Dabigatran 150 mg bid relative risk	0.26	0.14	0.49
Dabigatran 110 mg bid relative risk	0.31	0.17	0.56
Acetylsalicylic acid alone relative risk	0.55	0.20	1.41
Extracranial haemorrhage:			
Warfarin risk	2.88		
No treatment relative risk	0.55	0.14	1.75
Aspirin/clopidogrel relative risk	1.12	0.64	2.01
Dabigatran 150 mg bid relative risk	1.06	0.91	1.22
Dabigatran 110 mg bid relative risk	0.94	0.80	1.09
Acetylsalicylic acid alone relative risk	1.14	0.57	2.22
Age adjustment (>=80)	0.50	0.12	0.90
Minor bleeds:			
Warfarin risk	16.37		
No treatment relative risk	0.53	0.33	0.87
Aspirin/clopidogrel relative risk	1.25	0.49	2.50
Dabigatran 150 mg bid relative risk	0.91	0.86	0.97
Dabigatran 110 mg bid relative risk	0.79	0.74	0.84
Acetylsalicylic acid alone relative risk	0.64	0.30	1.28

Event	Rate/relative risk	95%LCI	95%UCI
Acute myocardial infarction risks:			
Warfarin risk	0.64		
No treatment relative risk	1.46	0.66	3.23
Aspirin/clopidogrel relative risk	1.33	0.54	3.15
Dabigatran 150 mg bid relative risk	1.27	0.94	1.71
Dabigatran 110 mg bid relative risk	1.29	0.96	1.75
Acetylsalicylic acid alone relative risk	1.60	0.91	3.23

Table 2. Post-event patient status by therapy and event.[30,31,33]

	Independent	Moderate disability	Totally dependent	90-day mortality
Stroke:				
Warfarin	53.9%	19.7%	4.3%	22.2%
No treatment	41.3%	18.5%	7.7%	32.5%
Aspirin/clopidogrel	53.9%	19.7%	4.3%	22.2%
Dabigatran 150 mg bid	57.7%	15.7%	1.6%	25.1%
Dabigatran 110 mg bid	48.0%	24.2%	6.8%	21.1%
Acetylsalicylic acid alone	51.4%	18.0%	6.7%	23.9%
Haemorrhagic stroke/intracranial haemorrhage:				
Warfarin	7.8%	8.8%	31.8%	51.6%
No treatment	15.1%	16.3%	42.8%	25.9%
Aspirin/clopidogrel	15.1%	16.3%	42.8%	25.9%
Dabigatran 150 mg bid	7.8%	8.8%	31.8%	51.6%
Dabigatran 110 mg bid	7.8%	8.8%	31.8%	51.6%
Acetylsalicylic acid alone	15.1%	16.3%	42.8%	25.9%

price bulletin issued by the Greek Ministry of Health.[41] As the analysis was undertaken from a payer perspective, the daily cost was based on retail price minus the patient co-payment. The cost for INR monitoring in the case of warfarin and acenocoumarol was taken from two recent studies of the National School of Public Health that were undertaken in order to estimate the cost of managing AF patients and the cost of INR monitoring.[25,32] The first study was undertaken to compare different types of INR monitoring in 2006. It was found that the cost of INR monitoring per patient per year was between €548 to €604, depending on the method used, and that the reimbursement cost for payers was a portion of it, at €180 to €308. The other study was undertaken in 2010, and its purpose was to estimate the cost of managing AF patients with different drug strategies (rate versus rhythm control). In the rhythm-control group the annual cost of INR monitoring was estimated at €280, the cost of hospital visits also at €280, and the remaining follow-up cost at €1092. In the rate-control group the annual cost of INR monitoring was estimated at €322, the cost of hospital visits at €260, and the remaining follow-up cost at €1055. These annual follow-up figures are in line with those obtained in a recent European Society of Cardiology survey that included Greece.[16] Therefore, INR monitoring on average was assumed to cost €301 per patient on an annual basis. It was assumed that physician visits would take place anyway; hence these are attributed to the follow-up and not to the INR cost, an assumption that favours warfarin and acenocoumarol relative to dabigatran. However, for patients outside the target INR range two extra visits and corresponding tests were assumed. Also, even though it had only a marginal impact on results, for reliability reasons, for patients with INR >3 a 15% decrease in warfarin/acenocoumarol dosage was assumed, whereas for those with INR <2 an increase in dosage of 15% was assumed. The cost of follow up for independent patients was set at €336 per quarter, based on a recent study of the National School of Public Health,[32] and it was increased following a change in dependency status, based on ratios from the original modelling study.[31] The cost of death was obtained from the literature and was inflated to 2012.[42] The reimbursement costs of the events were obtained from an analysis of claims data from the Ministry of Health and are based on the latest reimbursement tariffs used by payers.[43] As noted earlier, they do not include overhead and salary costs, which account for about 40%-70% of total health care cost, depending on therapy, and this explains why they are lower compared to other countries, a fact that is against the more efficacious therapy.

Table 3. Cost inputs (in €) used in the analysis. Drug data are from the Ministry of Health[41,43] and co-payments are applied. In the probabilistic analysis event costs are assigned gamma distributions.

Drug cost per day:	
Acetylsalicylic acid	0.02
Acetylsalicylic acid + clopidogrel	0.99
Dabigatran 150 bid	2.68
Dabigatran 110 bid	2.57
Warfarin INR 2-3	0.04
Warfarin INR<2	0.05
Warfarin INR>3	0.04
Annual cost of warfarin monitoring:	
Within range	301
Outside range	397
Mean event cost:	
Ischaemic stroke: fatal	1191
Ischaemic stroke: independent	1191
Ischaemic stroke: moderate disability	1860
Ischaemic stroke: totally dependent	3408
Systemic embolism: fatal	2699
Systemic embolism: non-fatal	2426
Transient ischaemic attack	1118
Intracranial haemorrhage: fatal	1580
Intracranial haemorrhage: independent	1188
Intracranial haemorrhage: moderate disability	1122
Intracranial haemorrhage: totally dependent	2459
Haemorrhagic stroke: fatal	1793
Haemorrhagic stroke: independent	1348
Haemorrhagic stroke moderate disability	1273
Haemorrhagic stroke totally dependent	2791
Extracranial haemorrhage (non-brain): fatal	1428
Extracranial haemorrhage: non-fatal: non-GI	367
Extracranial haemorrhage (non-brain): non-fatal: GI	367
Minor bleed	245
Acute myocardial infarction: fatal	1428
Acute myocardial infarction: non-fatal	2458
Discontinuation of treatment w/ event	50
Treatment switch	25
Death from unrelated causes	1500
Follow up cost per three-month cycle:	
Independent w/o stroke history	336
Independent w/ stroke history	399
Moderate	815
Dependent	3144

GI – gastrointestinal

Analyses

The model was set up to estimate total patient lifetime drug, event and therapy cost, life years (LY) and quality-adjusted life years (QALYs) per treatment option. In this light, it is possible to estimate the incremental cost per QALY of the new therapy relative to the existing ones. One-way sensitivity analysis was undertaken to test the robustness of the results. In this context, important variables were varied within specified ranges. Moreover, to deal with uncertainty the model was set to run probabilistic analyses. Hence, baseline risks were assumed to have beta distributions, while relative risks were assumed to be log-normally distributed. Event costs and utilities were assumed to have gamma and beta distributions, respectively. Simulation modelling was used to run 1000 analyses to allow the construction of cost-effectiveness acceptability curves, which indicate the likelihood of the incremental cost per QALY falling below specified thresholds.

Results

The estimated expected number of events per 10,000 patients in each therapy arm is presented in Table 4. Dabigatran 150 mg twice daily was superior in comparison to other therapies as far as ischaemic stroke was concerned, followed by warfarin/acenocoumarol, dabigatran 110 mg twice daily dose, acetylsalicylic acid, and acetylsalicylic acid plus clopidogrel. However, dabigatran 110 mg twice daily was superior in terms of the number of systemic embolism, transient ischemic attack, stroke, and extracranial haemorrhage events. Finally, warfarin and acenocoumarol were superior in minimising the number of acute myocardial infarction events.

The results of the cost-effectiveness analysis are presented in Table 5. The total life time cost was lowest in the acetylsalicylic acid arm (€28,014), followed by warfarin (€30,618), acenocoumarol (30,683), acetylsalicylic acid and clopidogrel (€30,953), dabigatran 150 mg twice daily (€34,836), and dabigatran 110 mg twice daily (€35,614). Dabigatran 150 mg twice daily was associated with 10.01 QALYs, followed by dabigatran 110 mg twice daily (9.94), warfarin/acenocoumarol (9.64), acetylsalicylic acid alone (9.43), and acetylsalicylic acid plus clopidogrel (9.31). The incremental cost per QALY for dabigatran 150 mg twice daily relative to the other therapies ranged from €5547 to €11,762, while the incremental cost per QALY for dabigatran 110 mg twice daily relative to the other therapies ranged from €7398 to €16,437. Acetylsalicylic acid and dabigatran 150 mg twice daily dominated the remaining therapies, by either direct or extended dominance. The incremental cost per QALY of dabigatran 150 mg twice daily relative to aspirin, the least costly option, was €11,762. However, in the local guidelines warfarin and acenocoumarol are the recommended therapies, with the latter being the most commonly used option in the market. The incremental cost per QALY of dabigatran 150 mg twice daily was €11,400 relative to warfarin and €11,224 relative to acenocoumarol. These are well be-

Table 4. Number of events per 10,000 patients for each comparator.

	Dabigatran 110 mg bid	Dabigatran 150 mg bid	Warfarin/ acenocoumarol	Acetylsalicylic acid	Acetylsalicylic acid & clopidogrel
Ischaemic stroke:	6361	5746	6118	7887	8468
Fatal	2229	2185	2247	2781	2873
Independent	2325	2230	2316	3020	3364
Moderate disability	1296	965	1113	1429	1639
Totally dependent	511	365	442	657	592
Systemic embolism:	687	696	754	983	1358
Fatal	0	0	0	0	1
Nonfatal	686	696	754	982	1357
Transient ischaemic attack	1562	1714	1817	2326	2307
HS/ICH:	649	793	1422	864	880
Fatal	275	344	675	230	234
Independent	62	75	119	118	119
Moderate disability	73	88	140	137	140
Totally dependent	239	286	488	380	387
Extracranial hemorrhage	4868	5265	4910	5070	4978
Acute myocardial infarction:	1768	1759	1493	1935	1724
Fatal	20	20	17	21	19
Nonfatal	1748	1739	1477	1913	1704

HS – haemorrhagic stroke; ICH – intracranial haemorrhage.

Table 5. Results of the economic evaluation.

	Dabigatran 110 mg bid	Dabigatran 150 mg bid	Acenocoumarol	Warfarin	Acetylsalicylic acid	Acetylsalicylic acid & clopidogrel
Drug costs (€)	8655	8710	3213	3148	67	2935
Event costs (€)	2763	2811	2873	2873	2749	3073
Follow-up costs (€)	24,196	23,315	24,597	24,597	25,198	24,945
Total cost (€)	35,614	34,836	30,683	30,618	28,014	30,953
QALYs	9,94	10,01	9,64	9,64	9,43	9,31
ICER vs. dabigatran 150 mg	NA	Base	11,224	11,400	11,762	5547
ICER vs. dabigatran 110 mg	Base	NA	16,437	16,653	14,902	7398

low the widely used threshold of €40,000-€50,000 or the threshold of three times the per-capita income (€55,000[44]).

Furthermore, the one-way sensitivity analysis, presented in Tables 6 & 7, indicates that on most occasions the incremental cost-effectiveness ratios (ICERs) of the two dabigatran doses fell below €20,000 per QALY. This analysis indicates that the results remain stable relative to other therapy options when various parameters of the model are change, such as the cost of events, utilities associated with different states, the age of the AF population, and discount rates for outcomes. Finally, the results of the probabilistic analysis are presented in Figure 2, which shows the cost-effectiveness acceptability curve for dabigatran 150 mg twice daily relative to the alternatives. About 60% of ICERs of dabigatran 150 mg twice daily relative to warfarin and acenocoumarol, the main comparators, fall below the €40,000 threshold and 70% below the €55,000 threshold. These figures are somewhat lower for the dabigatran 110 mg twice daily option.

Discussion

In the present study, an economic evaluation was undertaken to compare, from a payer perspective, dabigatran relative to existing alternatives for the prevention of serious events in patients with AF in Greece. The analysis showed that dabigatran 150 mg twice daily reduced the cost of thromboembolic events, but overall it was a more expensive therapy compared to the alternatives. However, dabigatran at this dose was more effective in terms of QALYs gained, and thus has an acceptable incremental cost-effectiveness ratio relative to other therapies. Dabigatran 110 mg twice daily also represents a cost-effective option relative to the existing therapies. These results held true under extensive sensitivity and probabilistic analyses and are in

Table 6. One-way sensitivity analysis for ICER of dabigatran 150 mg bid.

		Variable		Acenocoumarol		Warfarin		Acetylsalicylic acid		Acetylsalicylic acid & clopidogrel	
Baseline parameters	Base case	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
Age	72	58	86	11.145	17.750	9.546	18.023	9.495	22.962	4712	10.247
Discounting rate health	3.5%	1.0%	6.0%	7308	15.888	7543	16.062	7954	16.537	3713	7828
Discounting rate cost	3.5%	1.0%	6.0%	16.636	9202	13.856	9343	14.447	9799	6892	4568
Utilities											
Independent without disability	0.81	0.65	1.00	13.995	8781	14.214	8919	16.633	8653	8015	4015
Independent with disability	0.65	0.46	0.81	11.467	10.652	11.646	10.819	10.822	12.458	4965	6058
Moderate disability	0.46	0.30	0.65	10.552	11.579	10.717	11.761	11.007	12.588	5140	5984
Dependent disability	0.30	0.10	0.46	10.243	11.695	10.403	11.879	11.006	12.277	5276	5685
Costs											
Fatal ischaemic stroke	1191	952	1429	11.004	11.000	11.177	11.172	11.694	11.661	5511	5480
Ischaemic stroke: independent	1191	952	1429	11.006	10.997	11.179	11.170	11.701	11.654	5523	5496
Follow-up: independent	336	0	403	14.397	10.325	14.570	10.497	14.945	11.026	7803	5036

Table 7. One-way sensitivity analysis for ICER of dabigatran 110 mg bid.

		Variable		Acenocoumarol		Warfarin		Acetylsalicylic acid		Acetylsalicylic acid & clopidogrel	
Baseline parameters	Base case	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
Age	72	58	86	13.977	18.995	14.156	19.270	12.059	22.838	6325	10.958
Discounting rate: health	3.5%	1.0%	6.0%	10.930	23.478	11.075	23.788	10.120	21.074	4956	10.445
Discounting rate: cost	3.5%	1.0%	6.0%	20.951	13.271	21.225	13.448	18.878	12.215	9588	5888
Utilities											
Independent without disability	0.81	0.65	1.00	20.674	13.092	20.947	13.265	21.427	10.950	10.834	5320
Independent with disability	0.65	0.46	0.81	15.874	16.766	16.084	16.988	13.089	16.867	6345	8484
Moderate disability	0.46	0.3	0.65	16.924	15.710	17.148	15.918	14.641	12.229	7100	7673
Dependent disability	0.30	0.1	0.46	15.470	17.123	15.674	17.349	14.215	15.498	7143	7526
Costs											
Fatal ischaemic stroke	1.191	952	1.429	16.347	16.346	16.563	16.562	14.918	14.883	7367	7335
Ischaemic stroke: independent	1.191	952	1.429	16.346	16.346	16.563	16.563	14.924	14.877	7379	7323
Follow-up: independent	336	0	403	17.707	16.075	17.924	16.291	16.899	14.502	8533	7115

line with those obtained elsewhere for other settings.

In particular, the reference study for the modelling approach investigated the cost-effectiveness of dabigatran etexilate sequential dosing (150 mg bid for patients <80 years and 110 mg bid for patients ≥80 years) versus warfarin and "real-world" prescribing (i.e. warfarin, aspirin, or no treatment, in a cohort of warfarin-eligible patients) from a Canadian payer perspective, for AF patients at moderate-to-high risk.[31] Over a lifetime, the ICER of dabigatran was $10,440 /QALY versus warfarin and $3962 /QALY versus "real-world" prescribing. Moreover, the ICER of the higher dose was $9041 and that of the lower $29,994 per QALY. Another recent study employed a Markov model to estimate results for the USA.[45] The aim was to estimate the quality-adjusted survival, costs, and cost-effectiveness of dabigatran compared with adjusted-dose warfarin for preventing ischemic stroke in patients 65 years or older with non-valvular AF. The incremental cost-effectiveness ratios compared with warfarin were $51,229 per QALY for the lower dose of dabigatran and $45,372 per QALY for the higher dose of dabigatran. This model was sensitive to the cost of dabigatran, but was relatively insensitive to other model inputs. The cost-effectiveness of the higher dose of dabigatran improved with increasing risk for stroke and intracranial haemorrhage. Moreover, in a subsequent letter the incremental cost per QALY ratio of dabigatran was estimated at $12,400 for the 150 mg twice daily dose.[46]

In the USA, the cost-effectiveness of dabigatran 150 mg twice daily for secondary stroke prevention in

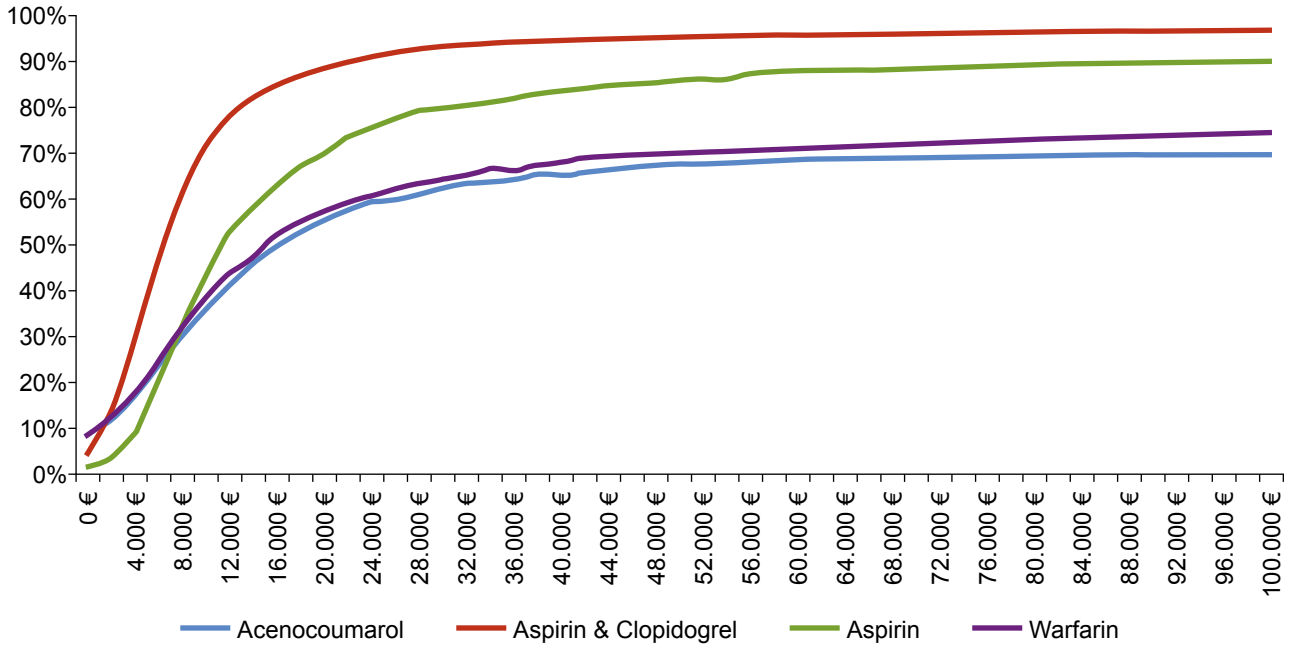

Figure 2. Cost-effectiveness acceptability curve of dabigatran 150 mg bid versus alternatives.

patients with AF and prior stroke or transient ischemic attack was also assessed in another study,[47] on the basis of a Markov decision model using data from the RE-LY trial and other sources. The target population was a cohort of patients aged 70 years with non-valvular AF, prior stroke, or transient ischemic attack, and no contraindication for anticoagulation. In the base case, dabigatran was associated with an incremental cost-effectiveness ratio of $25,000 versus warfarin. In sensitivity analyses, the cost-effectiveness of dabigatran was inversely related to the quality of INR control achieved with warfarin therapy. In Monte Carlo analysis, dabigatran was cost-effective in 57% of simulations using a threshold of $50,000 per QALY and 78% of simulations using a threshold of $100,000 per QALY. As in the previous studies, the investigators concluded that dabigatran appears to be cost-effective relative to warfarin for stroke prevention in patients with AF and prior stroke or transient ischemic attack.

Another study also investigated alternatives for stroke prophylaxis in patients with AF using various antithrombotic therapies, based on a Markov model in a hypothetical cohort of 70-year-old patients with AF using a cost-effectiveness threshold of $50,000 per QALY.[48] The authors concluded that, for a patient with an average risk of major haemorrhage (3% per annum), the most cost-effective therapy depended on stroke risk. For patients with the lowest stroke rate ($CHADS_2$ stroke score of 0), only acetylsalicylic acid was cost-effective. For patients with a moderate stroke rate ($CHADS_2$ score of 1 or 2), warfarin was cost-effective unless the risk of haemorrhage was high or the quality of INR control was poor. For patients with a high stroke risk ($CHADS_2$ stroke score 3), dabigatran 150 mg twice daily was cost-effective unless INR control was excellent. Warfarin was cost-effective in moderate-risk AF populations unless INR control was poor.[48] It is worth mentioning that, in the US, only the 150 mg twice daily approach has regulatory approval for dabigatran; thus, only the cost-effectiveness findings for this dose are relevant in the US setting.

Another study tried to determine the incremental net health benefits of dabigatran etexilate and warfarin in patients with non-valvular AF in the United Kingdom.[49] The study used a discrete event simulation model to extrapolate the findings of the RE-LY study to a lifetime horizon of patients from the perspective of the NHS. Population cohorts of 50,000 simulated patients at moderate-to-high risk of stroke, with a mean baseline $CHADS_2$ score of 2, were studied. In the economic analysis, the 150 mg twice daily dabigatran option had an incremental cost effectiveness ratio of £23,082 per QALY gained versus warfarin, and was more cost-effective in patients with a baseline $CHADS_2$ score of 3 or above. However, for good INR control, the higher dabigatran dose was not cost-effective, at £42,386 per QALY gained. Thus, the study concludes that dabigatran offers a positive bene-

fit-to-harm ratio when compared with warfarin. However, this model assigned an event disutility for intracranial bleeding that was more than 4 times lower than the one applied for stroke and assigned no long-term costs after this event, which does not appear to be justified, given that these events are so devastating. Finally, in another recent cost-effectiveness modelling study in the UK setting, dabigatran was compared relative to warfarin, acetylsalicylic acid or no therapy. Two patient cohorts with AF (starting age of <80 and ≥80 years) were considered separately, in line with the UK labelled indication. For patients initiating treatment at ages <80 and ≥80 years, the ICERs for dabigatran etexilate were £4831 and £7090 /QALY gained versus warfarin, with a probability of cost-effectiveness at £20,000 /QALY gained of 98% and 63%, respectively. For the patient cohort starting treatment at ages <80 years, the ICER versus acetylsalicylic acid was £3457 / QALY gained and dabigatran etexilate was dominant (i.e. was less costly and more effective) compared with no therapy. The authors concluded that the use of dabigatran etexilate as a first-line treatment for the prevention of stroke and systemic embolism is likely to be cost-effective in eligible UK patients with AF.

From the above, it is clear that our study's results are in line with those published in the literature in relation to other settings. Dabigatran was cost-effective relative to warfarin and other treatments for AF patients at medium-to-high risk of events. When new treatments are approved for use in health-care systems information is often limited; thus, models like the one presented here constitute the only option for evaluating their economic and health outcome impact. The analysis was based on an adaptation of an international model following certain methodological standards and is in line with others in the literature. However, it still suffers from several limitations and it should be viewed in that light. It does not represent experimental research, but instead it is based on a synthesis of data reported in the literature. Thus, although the methodology adopted followed the standard recommendations, it cannot substitute for real-life direct comparisons amongst the alternative treatments. Hence, post-launch observational studies are needed to verify the conclusions obtained from analyses such as the present one. A more complete analysis of real-world efficacy and real-world prescribing behaviour, as well as a broader (societal) analysis may be worthwhile. True health-care and patient direct and indirect costs are higher than those used here, and therefore the cost-effectiveness of the new therapy may be more favourable from a societal perspective.

Conclusion

Dabigatran, at both dosages, represents from a payer perspective a cost-effective treatment option for the prevention of stoke in moderate-to-high risk AF patients in Greece.

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