Economic appraisal of dabigatran as first-line therapy for stroke prevention in atrial fibrillation

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Background. Dabigatran is an oral anticoagulant direct thrombin inhibitor recently registered in South Africa (SA) to reduce the risk of stroke and systemic embolism in patients with atrial fibrillation (AF). Owing to the price disparity between warfarin (the current gold standard for treatment of patients with AF) and dabigatran, we conducted an economic appraisal of the use of dabigatran compared with warfarin from a payer perspective in the South African private healthcare setting.
Objectives. To estimate the cost-effectiveness (CE) and budget impact of dabigatran compared with warfarin for the prevention of stroke in AF patients.
Methods. A previously published Markov model was populated with SA cost and mortality data to estimate the CE and budget impact analysis of dabigatran over a lifetime horizon. The model population consisted of a cohort of patients of whom those aged younger than 80 years used dabigatran 150 mg twice daily and those older than 80 years 110 mg twice daily. Modelled outcomes included total cost, quality-adjusted life years (QALYs) and incremental CE ratio (ICER), with the effectiveness measured by QALYs gained.
Results. Dabigatran compared with warfarin as first-line treatment was estimated to have an ICER of R93 290 and an average incremental cost per beneficiary per month of R0.39 over a 5-year period. Conservative assumptions were made regarding the number of international normalised ratio monitoring tests for patients on warfarin, and the ICER is estimated to decrease by as much as 15.7% under less stringent assumptions. A robust sensitivity analysis was also performed.
Conclusion. Dabigatran as first-line treatment compared with warfarin for the use of stroke prevention in patients with AF is deemed cost-effective when used in accordance with its registered indication in the SA private sector.

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In South Africa (SA), the risk of cerebrovascular disease is significant; it is estimated that approximately 240 strokes occur daily.[1] Worldwide, up to 3 million people per year suffer atrial fibrillation (AF)-related strokes.[2] SA patients with irreversible AF currently use warfarin as first-line treatment. Dabigatran (Pradaxa; Boehringer Ingelheim) is an oral anticoagulant with direct thrombin inhibitory action and was registered in SA in September 2012 for the prevention of cardioembolic stroke in patients with non-valvular AF.

The Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY)[3] trial was a non-inferiority trial with 2-year follow-up, comparing the use of dabigatran with warfarin in patients with AF who were at risk of stroke. A total of 18 113 people in 44 countries were enrolled and randomised into three treatment arms, two blinded dabigatran arms, using two fixed doses of dabigatran (110 mg twice daily and 150 mg twice daily), and a blinded, adjusted-dose warfarin arm. The primary study outcome was prevention of stroke or systemic embolism. The primary safety outcome was major haemorrhage. Secondary outcomes were stroke, systemic embolism and death rates.

Both dabigatran doses were non-inferior to warfarin in respect of the primary efficacy outcome. In addition, the 150 mg dose of dabigatran was superior to warfarin with respect to prevention of stroke or systemic embolism, and the 110 mg dose was superior to warfarin in respect of major bleeding. The RE-LY trial showed relative reductions of 9.5% and 34.3% in the risk of stroke or systemic embolism for twice-daily dabigatran 110 mg and 150 mg, respectively, compared with warfarin. All-cause mortality was reduced by 9.2% and 12% for the 110 mg and 150 mg doses of dabigatran, respectively, compared with warfarin.[3]

Internationally, economic appraisals were performed to evaluate the use of dabigatran for patients with AF. In an economic study in the USA, the estimated cost per quality-adjusted life year (QALY) gained proved cost-effective below a willingness-to-pay threshold of US$50 000 per QALY when comparing dabigatran 150 mg twice daily with warfarin. The cost-effectiveness (CE) was, however, dependent on the pricing of dabigatran in the USA.[4] Economic appraisals performed in the UK had similar results.[5]

In SA, the daily cost of dabigatran is significantly more than the cost of warfarin. Policy makers therefore need to understand the potential economic benefits that might be derived from the use of dabigatran compared with warfarin. Economic appraisals not only provide insight into the economic viability of substituting dabigatran for warfarin, but also assist in policy decision making. The objective of this study was to estimate the CE and budgetary impact of using dabigatran for stroke prevention in patients with AF in the SA private healthcare sector, thereby assisting in guiding policy.

Methods

Kansal *et al.*[5] designed a CE model based on the outcome of the RE-LY trial in 2010. The CE model simulates disease progression and estimates quality of life and incremental cost per QALY for patients with AF in SA.

The CE results were estimated using the sequential dose model setup, which ensures that patients aged <80 years receive 150 mg dabigatran twice daily and patients >80 years 110 mg twice daily. Warfarin-related outcomes from the RE-LY trial are referred to as trial-like warfarin in the CE model, and in the model base case we used this parameter for warfarin utilisation in patients with AF. The 'real-world' utilisation of warfarin in patients with AF, incorporating less stringent international normalised ratio (INR) testing and sensitivity, was investigated by comparing dabigatran with real-world warfarin as first-line treatment.

The CE model developed by Kansal *et al.*[5] was made available for adaptation to the SA private healthcare setting and populated with SA mortality and cost data. These are discussed under 'Inputs and assumptions' below.

A budget impact analysis (BIA) module was developed by the authors. The BIA module considers and compares a status quo scenario where only warfarin is used for stroke prevention in AF patients, and a new intervention scenario in which some of the AF patients receive dabigatran for stroke prevention. The BIA module is a dynamic model that incorporates the prevalence, incidence and mortality of AF patients in SA. The budget impact is estimated over 5 years and is expressed as the incremental cost per beneficiary per month (ICPBPM).

The CE model and BIA model results were estimated using the base-case scenario parameters as set out in Table 1. Table 1 also indicates the rationale for using these parameters as a base-case scenario.

Event costs used to populate the model were estimated using 2007 medical scheme claims data. The data included 2.1 million claim lines occurring between January 2000 and May 2007. The claims represent all patients who had a claim with a diagnosis code contained in chapter IX of the 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD 10) coding system. These claims were adjusted to 2011 values using medical inflation figures as published by Statistics South Africa.[6]

Event costs are defined as: (*i*) the costs of clinical events that are associated with a patient with AF, notably stroke, systemic embolism (SE) and transient ischaemic attack (TIA); and (*ii*) the costs of adverse events in patients on treatment for AF related to bleeding tendencies.

Event costs were estimated separately for patients who were physically independent (i.e. able to function independently of assistance from a caretaker or family member) after any event, patients who were only moderately physically dependent, and patients who were totally physically dependent. The model accounts for follow-up costs after a thromboembolic event based on patients' physical dependencies.

Inputs and assumptions

Mortality data

There are no publicly available life tables for the SA medically insured population. The SA85-90 life tables published by the Actuarial Society of South Africa[7] were used as an approximation for the mortality experience of the SA private sector. The mortality rate of the SA85-90 population is greater than the mortality rates used by Kansal *et al.*,[5] with the difference more pronounced in females than in males.

Drug costs

The cost of dabigatran was supplied by Boehringer Ingelheim SA (BI SA). It is assumed that patients with an INR of <2 will require 5 mg of warfarin per day, those with an INR within the range of 2 - 3, 3 mg of warfarin per day, and those with an INR of >3, 1 mg of warfarin per day. The costs of these drugs are set out in Table 2.

Event costs

The cost of ischaemic stroke (IS) was estimated by calculating the total claimed amount for any hospitalisation during which a patient had a claim reflecting stroke, not specified as haemorrhage or infarction. It was assumed that the median cost of the first quarter of the data is the average cost for a patient who is independent following an IS. Similarly, it was assumed that the cost for a patient who is moderately disabled following an IS is represented by the median cost of the second quarter of the sorted data, the cost of a fatal IS by the median of the third quarter of the data, and the cost for a patient who is totally dependent after an IS by the median of the last quarter of the data. Owing to a lack of robust data, it was assumed that intracranial haemorrhage (ICH), haemorrhagic stroke (HS) and IS all incurred the same cost. SE was estimated by calculating the total claimed cost in hospital, where at least one claim with pulmonary embolism occurred. The cost of fatal cases was estimated using the first quartile of the systemic event costs, and the non-fatal cases were estimated using the third quartile of the costs. A TIA was estimated as the median total hospital cost where at least one claim with TIA

Table 1. Base-case scenario parameters

Parameter	Input used	Rationale
Single-dose/sequential dose model	Sequential dose model	Dabigatran registered indication
Patient population	<80 RE-LY population	This allows patients to have a dose reduction when they reach age 80 years
Dabigatran indication in treatment sequence	1st line	Dabigatran registered indication
1st-line treatment comparator	Trial-like warfarin	High data quality
2nd-line treatment when dabigatran is 1st line	No treatment	Most conservative option
INR adjustment	Weighted warfarin approach	Calculates the percentage of patients with INR in and out of range and applies a risk adjustment to each category
Time horizon	Lifetime	Standard practice in CE modelling

INR = international normalised ratio; CE = cost-effectiveness.

Table 2. Model inputs

Drug cost per day (R)	
Dabigatran 110 mg bid	24.66
Dabigatran 150 mg bid	24.66
Warfarin INR <2	1.65
Warfarin INR 2 - 3	1.06
Warfarin INR >3	0.94
Event, *n*	
Fatal IS	39 353
IS, independent	10 056
IS, moderate disability	17 000
IS, totally dependent	75 865
SE, fatal	18 040
SE, non-fatal	72 472
TIA	15 900
ICH, fatal	39 353
ICH, independent	10 056
ICH, moderate disability	17 000
ICH, totally dependent	75 865
HS, fatal	39 353
HS, independent	10 056
HS, moderate disability	17 000
HS, totally dependent	75 865
ECH (non-brain), fatal	47 088
ECH (non-brain), non-fatal, non-GI	3 310
ECH (non-brain), non-fatal, GI	12 317
Minor bleed	3 310
Acute MI, fatal	78 869
Acute MI, non-fatal	78 869
Discontinuation of treatment following an event	0
Treatment switch	0
Death from unrelated causes	0
Follow-up costs per year (R)	
Follow-up – independent with stroke history	19 490
Moderate disability with stroke history	23 120
Dependent disability with stroke history	61 370
Treatment discontinuation without an event	378
Monitoring costs per test (R)	
INR monitoring	104.80
Specialist consultation	378.38

INR = international normalised ratio; IS = ischaemic stroke; SE = systemic embolism; TIA = transient ischaemic attack; ICH = intracranial haemorrhage; HS = haemorrhagic stroke; ECH = extracranial haemorrhage; GI = gastrointestinal; MI = myocardial infarction.

occurred. The cost of acute myocardial infarction (MI) was estimated as the median total cost in hospital where at least one claim with acute MI occurred, and it was assumed that fatal and non-fatal MIs have the same cost. Fatal extracranial haemorrhage (ECH) and non-fatal gastrointestinal (GI) bleeds were estimated from the total cost of hospital stay claims. It was assumed that discontinuation of treatment after an event, treatment switch and death from unrelated causes are not associated with additional costs. The event costs are summarised in Table 2.

A patient's follow-up costs subsequent to a stroke were estimated from costs incurred after the patient had been discharged from hospital. A zero cost was assumed when a patient was independent without a stroke history. It was assumed that treatment discontinuation without an event would result in the cost of one consultation. These costs are also summarised in Table 2.

Treatment uptake

The BIA module compares a cohort of AF patients using warfarin with the same cohort should they initiate treatment with dabigatran. The BIA module is based on the assumption that 3 333 AF patients will receive dabigatran for stroke prevention in year 1 (which comprised 20% of the total number of AF patients). Furthermore, it was assumed that the total number of patients receiving dabigatran will increase by 10% per annum. These assumptions are based on market growth projections provided by BI SA.

Warfarin monitoring costs

The INR monitoring cost of patients treated with warfarin is incorporated into the model. The costs for one INR test and one specialist consultation are shown in Table 2. Owing to lack of SA data, the INR testing frequency was estimated using medical schemes' claims data and verified by consultation with two key opinion leaders (KOLs). The claims data are shown in Fig. 1 and suggest a bimodal distribution, indicating that a large proportion of patients receive an INR test twice a month or more frequently, and another large proportion monthly. These two centroids are assumed to represent the average number of tests for uncontrolled and controlled patients. The KOLs agreed that controlled patients will have monthly INR tests, while the frequency of INR tests for uncontrolled patients can vary between daily and bimonthly.

Accordingly, for the base case, it was estimated that patients with an INR within the range of 2 - 3 would have an average of 12 INR tests per annum, while patients with an INR outside this range would have 24. These are thought to be conservative estimates, as many patients receive more than two INR tests per month (Fig. 1). It was assumed that patients with an INR within and outside the range of 2 - 3 will have three and six specialist consultations per year, respectively.

Results

Table 3 sets out the CE results for the base-case scenario with effectiveness measured by QALYs gained. Table 4 shows the BIA results.

Sensitivity analysis

The base-case scenario compared using dabigatran as first-line treatment with trial-like warfarin, with no treatment as second-line treatment.

The choice of comparator when dabigatran was used as a first-line option was altered between trial-like warfarin and real-world warfarin. The ICER decreases to R90 077 (-3.45%) and the ICPBPM decreases by 3.26% on average over a period of 5 years.

Sensitivity analysis was performed on INR monitoring. For the scenario in which a patient's INR falls outside the range, one of the KOLs advised that 'If on long-term warfarin, as many as 36 tests per year might be performed.' Sensitivity analysis on the number of INR tests for uncontrolled patients was therefore conducted and the ICER was estimated with 24 and 36 INR tests annually. The number of INR

Table 3. Base-case cost-effectiveness results

Treatment option	Drug costs (R)	Event costs (R)	Follow-up costs (R)	Total cost (R)	LYs	QALYs	ICER (R)
Dabigatran	60 365	23 426	236 496	320 286	9.33	7.19	93 290
Trial-like warfarin	24 243	24 888	252 119	301 249	9.14	6.98	

LYs = life years; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio.

Table 4. Base-case budget impact analysis results over a 5-year period

	Total cost (R)			
Year	Before dabigatran launch	After dabigatran launch	Incremental cost (R)	ICPBPM (R)
2012	354 331 177	369 022 581	14 691 404	0.15
2013	720 191 835	747 948 446	27 756 611	0.28
2014	1 095 201 218	1 135 134 295	39 933 077	0.40
2015	1 476 730 304	1 528 308 981	51 578 677	0.52
2016	1 861 716 479	1 924 686 994	62 970 514	0.63

ICPBPM = incremental cost per beneficiary per month.

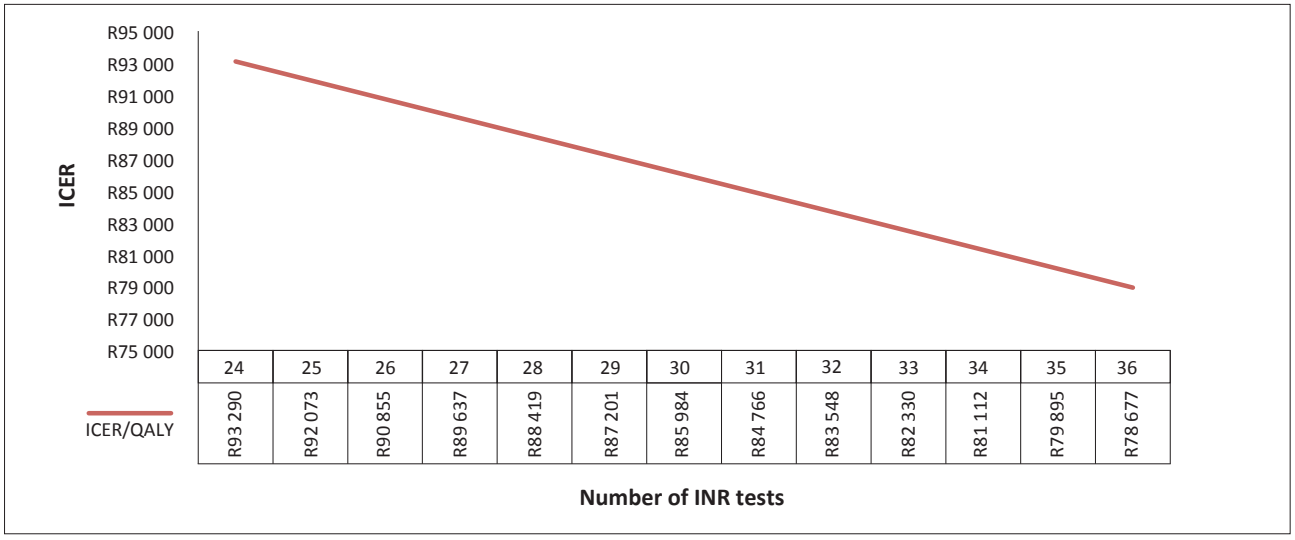

Fig. 1. Frequency of prothrombin tests for patients on warfarin estimated from medical scheme data. The red line indicates a smoothed kernel estimate for the distribution of international normalised ratio test frequency.

tests conducted, and the estimated ICER for uncontrolled patients per year, are shown in Fig. 2. The number of tests for a controlled patient was not altered from the base case. The ICER decreases by as much as 15.7% when increasing the number of INR tests for uncontrolled warfarin patients from 24 tests per annum to 36 tests per annum.

The BIA results for an uncontrolled warfarin patient, assuming that these patients receive 30 and 36 INR tests per year, indicate that the ICPBPM ranges between R0.14 and R0.60 for 30 INR tests and between R0.13 and R0.56 for 36 tests. The relative reductions from the base case are 4.7% and 9.4% in the first year for 30 and 36 INR tests, respectively. The average decreases of the ICPBPM over 5 years are 5.2% and 10.5%, respectively.

In the opinion of the KOLs, a stable individual can use up to 20 mg of warfarin a day; sensitivity analysis was therefore also performed on the amount of warfarin used by a patient within the INR range 2 - 3 and that for a patient whose INR is <2. The amount was adjusted to

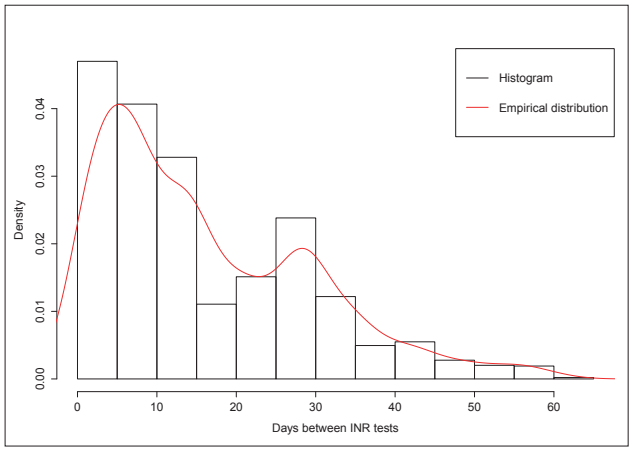

Fig. 2. Incremental cost-effectiveness ratio when the number of international normalised ratio tests for an uncontrolled patient on warfarin increases.

20 mg a day from 3 mg for a patient within range and from 5 mg for a patient with an INR <2. For a patient with an INR >3, warfarin use remained at 1 mg a day. The ICER decreases to R27 055, representing a 71% reduction from the base-case results. The estimated BIA results reveal an average decrease of 48% over a period of 5 years, ranging from R0.08 in year 1 to R0.32 in year 5.

Discussion

In this study, we first estimated the CE of dabigatran as first-line treatment compared with warfarin, followed by no second-line treatment. Secondly, the budgetary impact of introducing dabigatran into the SA private healthcare market over a 5-year period was investigated. CE was demonstrated for patients using 150 mg of dabigatran twice daily if aged <80 years, after which they will switch to 110 mg dabigatran twice daily. The analysis estimated the total cost for dabigatran and warfarin, as well as the life years and QALYs for both treatment arms, to calculate the ICER with effectiveness measured by QALYs gained.

At an ICER of R93 290, dabigatran proves cost-effective when compared with trial-like warfarin as a first-line treatment in patients with AF and at risk of suffering IS. The budgetary impact was estimated as R0.15 per beneficiary per month in the first year, increasing to R0.63 in the 5th year. Although this appears to be small, it should be considered by policy makers and healthcare funders as part of their total budget, the burden of disease of their respective risk pools and the potential opportunity cost of funding dabigatran in the future.

The authors considered various clinical scenarios (through sensitivity analyses) to estimate the CE and budgetary impact of treating AF patients with dabigatran as first-line therapy for stroke prevention.

It was observed that the results are not very sensitive to the comparator in first-line treatment when using trial-like or real-world warfarin. The base-case results are considered to be conservative, since the cost offset by avoidance of INR testing through the use of dabigatran reduces the ICER by up to 15.7% under less conservative assumptions. The base-case scenario is also sensitive to an increase in the amount of warfarin used by a patient according to the INR range.

Comparing the model inputs used by Kansal *et al.*,[5] and the inputs used to populate the model for the SA private sector, the largest relative cost difference was shown for a patient being independent, moderately disabled and totally dependent as a result of IS, IH and HS. The mortality rates used by Kansal *et al.* were lower than the mortality rates used for the SA health sector. Mortality rates in SA are on average 23% and 27% higher for males and females, respectively, than those in the UK model. This together with the cost differences influenced the results generated for the SA population.

The National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance[8] showed that the INR monitoring costs for the population on warfarin are difficult to quantify accurately. This is due to the variation in the costs of INR testing in the UK, as well as uncertainty about the frequency of INR testing, which is dependent on the patient's INR range. NICE made a key recommendation that dabigatran be recommended as a treatment option for the prevention of strokes in patients with AF, within the licensed indications of use. Furthermore, NICE agreed that a dose of 150 mg was clinically more effective in the RE-LY trial.

We conclude that dabigatran should be considered as a cost-effective option within its registered indication when compared with warfarin. Accurate data on the resource utilisation (specifically frequency of INR testing) associated with stroke prevention in AF will enhance the robustness of the results. Dabigatran is worthy of consideration as a treatment option when managing patients with AF, as it is the only treatment that, when compared with warfarin, provides a superior reduction in IS and HS, which is the main goal of anticoagulation treatment.

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