Systematic Review
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WHAT INFLUENCES THE COST EFFECTIVENESS OF DABIGATRAN VERSUS WARFARIN FOR STROKE PREVENTION IN ATRIAL FIBRILLATION: A SYSTEMATIC REVIEW

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ABSTRACT

Objectives

The introduction of new oral anticoagulants for the prevention of stroke in atrial fibrillation (AF) has changed the clinical management of AF. To inform decision making around dabigatran by identifying factors influencing cost-effectiveness results, we undertook a systematic review of economic evaluations of dabigatran versus warfarin for the prevention of stroke in AF patients.

Methods

A systematic literature search of Ovid Medline and Embase, Wiley's Cochrane Library, HEED, PubMed databases and grey literature was carried out for primary economic evaluations comparing dabigatran versus warfarin in patients with AF. Data on study characteristics, model inputs and results, and sensitivity analyses were abstracted and synthesized qualitatively.

Results

Twenty-three economic evaluations were identified and RE-LY was cited in 52% of studies as the source of the efficacy data. Twenty evaluations used Markov modelling, 2 performed discrete event simulation, and 1 was a trial-based evaluation. Eighty-two percent reported base case incremental cost-effectiveness ratios (ICERs) of less than $50,000 USD/QALY. Key variables, including international normalized ratio (INR) control, the cost of monitoring, risk of stroke and bleeding, and age were found to alter the conclusions in only a few studies. Less commonly explored factors included time horizon and cost of long-term care follow-up.

Conclusions

Several factors should be considered when interpreting the results of economic analyses which are based on randomized clinical trial evidence. Real-world data are needed to further assess the clinical and economic consequences of dabigatran relative to warfarin for the prevention of stroke in AF.

Keywords: *dabigatran, warfarin, atrial fibrillation, cost-effectiveness, systematic review*

Atrial fibrillation (AF) is a cardiac arrhythmia, which is associated with significant clinical and economic burden worldwide. This burden includes both acute care of AF and the downstream costs of clinical events such as stroke and systemic embolism (SE). As the prevalence of AF increases with age,[1] there is continuous, substantial and increasing impact on health care systems worldwide. In 2010, the global age-adjusted prevalence of this disease was 596.2 and 373.1 per 100,000 men and women, respectively.[2] It

is therefore a clinical and economic imperative to manage AF and prevent subsequent events.

For decades, the treatment of choice for the prevention of stroke and SE in AF patients was anticoagulation using vitamin K antagonists (VKAs), primarily warfarin.[3] VKAs, however, have a narrow therapeutic range and require regular monitoring by blood tests aiming for a therapeutic international normalized ratio (INR); they interact with some foods and drugs; their main adverse effect is bleeding which can be severe or fatal; and reversal of anticoagulation is required for any major procedure or bleed.[4] These limitations of VKAs led to the development of new direct oral anticoagulants (DOACs), the first of which was dabigatran.[5]

RE-LY was a large multinational randomized trial that concluded that 2 doses of dabigatran (150 mg and 110 mg twice a day) were non-inferior to warfarin.[6] Based on the data from the RE-LY trial, dabigatran was approved in multiple countries during 2010–2011.[7–9] In 2013, in the US, dabigatran represented 44% of all new oral anticoagulant prescriptions.[10] Overall, new oral anticoagulants (i.e., dabigatran, rivaroxaban, and apixaban) accounted for 62% of all new anticoagulants prescriptions and 98% of the costs associated with the anticoagulant class.[10] The 6-month initiation cost per patient increased from $54 with warfarin to $205 with dabigatran, and $221 for rivaroxaban. This study also found that the use of oral anticoagulants (warfarin, dabigatran, rivaroxaban and apixaban) were associated with lower CHADS and HAS-BLED scores,[10] which is different from the use of these agents in the pivotal randomized clinical trials (RCTs) such as RE-LY. In addition, shortly after its release, dabigatran became the leading source of drug-related serious harm reported to FDA,[11] providing a firm reminder that all anticoagulants cause bleeding. Limited emerging availability of antidotes globally for bleeding due to dabigatran, or a quantitative anticoagulation test (as the INR is for warfarin) to assure medication adherence, has raised concerns that real-world use might lead to different cost-effectiveness estimates than the RCTs.

Several early systematic reviews of the cost-effectiveness of dabigatran and other DOACs have found these agents to be cost effective, largely based on the Phase 3 trial information.[12–16] Two were limited by the small number of economic studies reviewed[13,16] and the other 3 were descriptive in nature, providing little information on the factors influencing the cost-effectiveness results.[12,14,15] Given the rapid uptake of DOACs, their use in subgroups not well represented in the Phase 3 trials, and the rapidly increasing, huge costs of anticoagulation, decision makers understandably may wish to revisit the economic evaluations to analyse whether the models used an appropriate breadth and depth of assumptions.

Our objective was to systematically review all of the available economic evaluations of dabigatran versus warfarin, with a focus on critically appraising the key factors influencing the cost-effectiveness results of these studies.

METHODS

Systematic Literature Search

The literature search was developed by an information specialist in consultation with the review team and conducted in March 2014. The following databases were searched: Ovid Medline (1946-present; In-Process & Other Non-Indexed Citations); OvidEmbase (1980-2014 week 10); Wiley's Cochrane Library & HEED; PubMed (for non-Medline records), as well as grey literature. Both controlled vocabulary terms such as the NLM's MeSH (Medical Subject Headings) and keywords were used. Searches were not restricted to any language. A methodological filter was applied to limit retrieval to economic evaluations. All search results were imported into a Reference Manager Version 12 database for the purposes of removing duplicate citations and title/abstract screening. The references of key publications were also reviewed. Online Resource I presents the detailed search strategy for Ovid Medline and Embase.

Study Selection

Two reviewers independently screened the titles and abstracts using pre-defined eligibility criteria. One reviewer then independently evaluated the full-text version of all included articles and a second reviewer screened the full text of a 20% random sample. To be included, articles had to meet the following criteria: trial-based or model based economic evaluation published in English addressing both costs and outcomes;

compared dabigatran versus any VKA[17]; and addressed a patient population with AF, with or without prior history of stroke, who were at an increased risk of stroke and SE. Economic evaluations available only in abstract form were excluded along with other types of publications such as cost analyses, budget impact analyses, surveys, editorials, and reviews.

Data Abstraction

Data were abstracted directly into a Microsoft Excel workbook using pre-defined data abstraction forms. Data elements captured included study design, setting, comparators, model type and time horizon, cycle length and perspective, clinical events, rates and data sources; drug costs, monitoring costs for warfarin and dabigatran, event and long-term follow-up costs; economic and clinical results; sensitivity analyses, and conclusions. Abstracted data were verified for accuracy and completeness for all of the included studies.

Synthesis

Synthesis of economic results focused on the cost-effectiveness of dabigatran as either sequential dosing or 150 mg twice daily compared to warfarin. Sequential dosing was defined as dabigatran 150 mg twice a day until the age of 80, after which the dose was reduced to 110 mg twice a day. In studies in which the economic results were not presented but adequate data were available, incremental cost-effectiveness ratios (ICERs) were calculated. For ICERs, all currencies were converted to 2014 US dollars (May 13, 2014) using the Bank of Canada daily currency converter[18] and consumer price index for medical care from the US Bureau of Labor Statistics.[19] To determine if an intervention was cost effective, 2 commonly cited thresholds for economic evaluations were used. ICERs less than $50,000/QALY gained[20] and less than $100,000/QALY gained,[21] were deemed cost effective. Since economic evaluations cannot be synthesized quantitatively, a qualitative analysis and summary is presented.

RESULTS

Literature Search Results

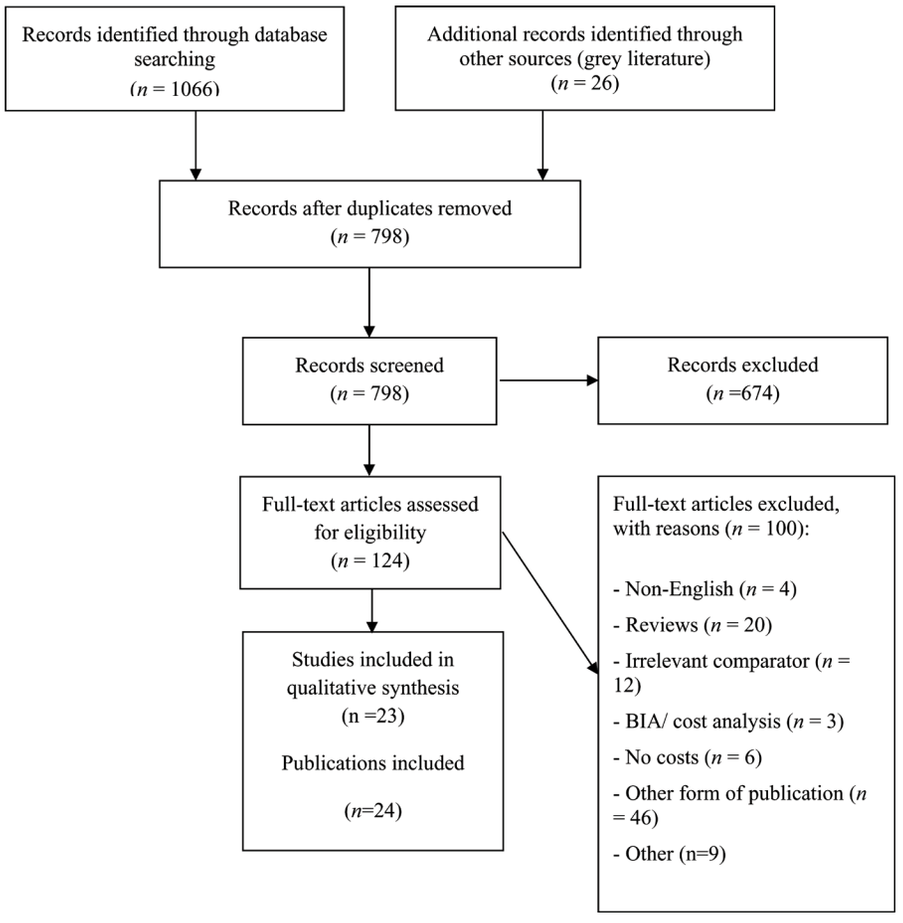
We identified 1,066 citations through database searching and 26 citations through grey literature. After removal of duplicates, 798 citations were screened, 124 articles went through full-text review, and 24 publications of 23 economic evaluations were included in the qualitative synthesis. Figure 1 outlines the flow diagram of included studies.

Study Characteristics

Table 1 describes the characteristics of the included studies. Of the 23 economic evaluations, 7 studies were based on country specific adaptation of the dabigatran manufacturer-sponsored Markov model developed by Sorensen et al.[22] and one study was a trial-based economic evaluation.[23] Almost half of the studies were conducted in the North American setting, the remainder in Europe. Due to country differences, dosing for dabigatran varied between studies (i.e., 110 mg, 150 mg, sequential). With the exception of two studies[24,25] which used discrete event simulation (DES) techniques, all the economic evaluations were based on Markov models. Compared to Markov models, DES modelling provides more flexibility in modelling health states and patients trajectories.[26] Most studies used a lifetime time horizon and adopted a payer perspective for their analysis. The mean age of the populations being modelled ranged between 65 and 80 years of age depending on the study. Fifty-two percent of the evaluations used the RE-LY trial[6] as the basis for their evaluations[5,22,24,27–36] while other studies[23,25,37–45] used hypothetical AF cohorts with moderate to high risk of stroke based on $CHADS_2$ scores or other criteria. Of the 19 studies reporting sources of funding, 8 (42%) were industry sponsored (Boehringer Ingelheim),[22,27,28,31–33,35,28] and all but one of these was based on the Sorensen model.[38]

In terms of model structure, the mean number of health states per model was 7 and ranged from 5[42,45] to 9.[22,23,28,30–33,35] The latter studies included ischemic stroke (IS), transient ischemic attack, myocardial infarction (MI), SE, hemorrhagic stroke (HS), intracranial hemorrhage (ICH), extracranial hemorrhages (ECH), gastrointestinal (GI) bleeds, minor bleeds, and death. Five health states (IS, MI, ICH, ECH and death) were common to all 20 Markov models. In some cases GI and non-GI bleeds were classified under ECH,[37] while other studies only reported major bleeds.[43] With respect to clinical outcomes projected by the models, inconsistency in the measure of effectiveness

FIG. 1 PRISMA flow diagram of included studies



(e.g., event rate per 100 patient-years versus major events per 10,000 patients) and limited reporting of results prevented any comparison between the studies (Online Resource II).

A key assumption around AF modelling is related to INR monitoring and Time in Therapeutic Range (TTR). When reported,[22,30–33,35,36,41,41] TTR values were based on the RE-LY study (i.e., 64%) (Table 2). Many studies, however, did not present the assumptions around anticoagulation management including INR monitoring for warfarin, degree of INR control (i.e., TTR), and health care resource utilization associated with monitoring warfarin and dabigatran. For example, while it is expected that INR testing will result in extra health care utilization for warfarin, 48% of the studies did not provide information on assumptions for the number of INR tests[5,22–25,27,29,31,32,40,42,44] and 65% on family doctor visits per year.[22–25,27,30–31,36,39–42,44,45] The recommended frequency of laboratory monitoring (renal function) or dose adjustments needed for dabigatran were not clear early after its release. However, almost half of the studies[22,32–35,37–41,45] included costs for a range of family doctor visits (e.g., every 6 months or every year) or specialist visits to manage dabigatran treatment.

Cost-Effectiveness Results

Twenty-two studies presented results in terms of incremental costs per quality-adjusted life years (QALY) gained and 11 studies also presented analyses in terms of incremental cost per life year gained (LYG). As shown in Table 3, there was large variation in costs and QALYs generated due to different methodologies (e.g., lifetime vs. 5-year time horizon; payer vs. societal perspective) or settings (e.g., country). However, even when analyses were conducted in the same country

TABLE 1 Characteristics of Studies Included in the Review

Author Year	Country Setting	Comparators of Interest	Model Type, Time Horizon, Cycle Length	Perspective	Mean Age, (years)	Patient Population (AF type, $CHADS_2$, inclusion/exclusion criteria)	Study Sponsor
Markov Models based on Sorensen 2011							
Sorensen, 2011[22]	Canada	1) Sequential dabigatran* 2) Dabigatran 150mg 3) Dabigatran 110mg 4) Trial-like warfarin 5) Real-world prescribing (warfarin, aspirin, or no treatment)	Markov model; lifetime; 3-month	Health care	69	Matched RE-LY trial. Hypothetical cohort of AF patients: ≥1 risk factor for stroke/embolism or impaired left ventricular ejection fraction (mean $CHADS_2$ =2.1); no contraindications to anticoagulation and not on any concomitant anticoagulation medicine	Boehringer Ingelheim Canada
González-Juanatey, 2012[30]	Spain	First scenario: 1) Sequential dabigatran* 2) Warfarin Second scenario: 1) Sequential dabigatran 2) Prescribing pattern (60% vitamin K antagonist; 30% aspirin; 10% no treatment)	Markov model; lifetime; 3-month	Health care	69.1	Hypothetical cohort of 10,000 patients; non-valvular AF with no disability; simulated patient profile to RE-LY population	NR
Kansal, 2012[31]	UK	1) Sequential dabigatran* 2) Adjusted-dose warfarin (with trial-like INR control) 3) Aspirin 4) No treatment	Markov model; lifetime; 3-month	NR	NR	Matched RE-LY trial. Hypothetical cohort; AF patients ≥ 1 risk factor for stroke/embolism or impaired left ventricular ejection fraction (mean $CHADS_2$ =2.1)	Boehringer Ingelheim
Langkilde, 2012[32]	Denmark	1) Sequential dabigatran* 2) Warfarin	Markov model; lifetime; 3-month	Health care	69	Hypothetical cohort of 10,000 patients; patient risk profile similar to RE-LY trial < 80 years	Boehringer Ingelheim, Denmark

(*Continues*)

TABLE 1 (*Continued*)

Author Year	Country Setting	Comparators of Interest	Model Type, Time Horizon, Cycle Length	Perspective	Mean Age, (years)	Patient Population (AF type, $CHADS_2$, inclusion/exclusion criteria)	Study Sponsor
Andrikopoulos, 2013[27]	Greece	1) Dabigatran 150mg 2) Dabigatran 110mg 3) Adjusted-dose warfarin 4) Acenocoumarol 5) Acetylsalicylic acid monotherapy 6) Acetylsalicylic acid + clopidogrel	Markov model; lifetime; 3 months	Health care	NR	RE-LY trial: non-valvular AF patients, primarily at moderate-to-high risk of stroke or embolism and eligible for anticoagulation treatment	Boehringer Ingelheim Hellas
Bergh, 2013[28]	South Africa	1) Sequential dabigatran* 2) Trial-like warfarin 3) No treatment	Markov model; lifetime; cycle NR	Private health care	< 80	RE-LY trial population	Boehringer Ingelheim
Pletscher, 2013[33]	Switzerland	1) Sequential dabigatran* 2) Dabigatran 150mg 3) Dabigatran 110mg 4) Phenprocoumon	Markov model; lifetime; 3-month	Health care	71 non-sequential; 69.1 sequential	Hypothetical cohort of 10,000 AF patients; subsamples of the RE-LY trial	Boehringer Ingelheim
Wouters, 2013[35]	Belgium	1) Sequential dabigatran* 2) Adjusted-dose warfarin (with trial-like INR control)	Markov model; lifetime; 3-month	Health care	69	Hypothetical cohort of 10,000 patients; non-valvular AF patient risk profile as RE-LY trial (< 80 years at baseline)	SCS Boehringer Ingelheim Comm V
Other Markov Models							
Freeman, 2011[39]	USA	1) Dabigatran 150mg 2) Dabigatran 110mg 3) Warfarin	Markov model; lifetime (max 35 years or death); cycle NR	Societal	≥ 65	Hypothetical cohort; non-valvular AF with increased risk for stroke ($CHADS_2$ ≥1), no contraindications to anticoagulant therapy	AHA; VA Health Services Research & Development Service
Shah, 2011[43]	USA	1) Dabigatran 150mg 2) Dabigatran 110mg 3) Warfarin 4) Aspirin plus clopidogrel 5) Aspirin 6) No therapy	Markov model; 20 years; 1-month	Third-party payer	70	Hypothetical cohort; AF with moderate risk of stroke and no contraindication to anticoagulant therapy	AHA; Knowlton Foundation; Fellowship at Washington University in St. Louis

Davidson, 2012[38]	Sweden	1) Sequential dabigatran* 2) Warfarin	Markov model; 20 years; cycle NR	Societal	65	Patients with AF	Boehringer Ingelheim and the County council of Ostergotland, Sweden
Kamel, 2012[41]	USA	1) Dabigatran 150 mg 2) Adjusted-dose warfarin	Markov model; 20 years or death; 30 days	Societal	≥ 70	Hypothetical cohort; non-valvular AF, prior stroke or TIA and no contraindications to anticoagulant therapy	NR
Wells, 2012[5]; Coyle, 2013[29]	Canada	1) Dabigatran 150 mg 2) Dabigatran 110 mg 3) Warfarin 4) Apixaban 5) Rivaroxaban 6) Sequential dabigatran* (*sensitivity analysis*)	Markov model; lifetime (max 40 years); 3-month	Health care	72	Non-valvular AF requiring anticoagulation; typical patient profile from RE-LY with no previous stroke or MI	Canadian Institute Health Research (CIHR) Drug Safety and Effectiveness Network (DSEN)
You, 2012[36]	USA	1) Dabigatran 150mg 2) Dabigatran 110mg 3) Genotype-guided AC (warfarin) 4) Usual AC (warfarin)	Markov model; 25 years; 1-month	Health care	≥ 65	Patient profile adopted from RE-LY trial; with high risk for stroke ($CHADS_2$ score ≥2)	No project funding received
Canestaro 2013[37]	USA	1) Dabigatran 150mg 2) Warfarin 3) Rivaroxaban 4) Apixaban	Markov model; lifetime; 1-month	Societal	70	Cohort of warfarin eligible patients with AF and average $CHADS_2$ score of 2	CVS Caremark
Harrington, 2013[40]	USA	1) Dabigatran 150mg 2) Adjusted-dose warfarin 3) Rivaroxaban 4) Apixaban	Markov model; 30 years or death; 1-month	Societal	70	Hypothetical cohort; patients with non-valvular AF, increased risk for stroke, a renal creatinine clearance of ≥ 50mL/min and no previous contraindications to anticoagulant therapy	NR

(*Continues*)

TABLE 1 (*Continued*)

Author Year	Country Setting	Comparators of Interest	Model Type, Time Horizon, Cycle Length	Perspective	Mean Age, (years)	Patient Population (AF type, $CHADS_2$, inclusion/exclusion criteria)	Study Sponsor
Nshimyumukiza, 2013[42]	Canada	1) Dabigatran 150 mg 2) Warfarin genetic-guided dosing 3) Warfarin standard dosing	Markov model; 5 years or death; daily	Health care	64	Hypothetical population of 10,000 individuals with new AF diagnosis and no previous stroke or contraindication to anticoagulation therapy	CIHR; APOGEE-Net/ CanGeneTest Research and Knowledge Network in Genetic Health Services
Rognoni, 2014[34]	Italy	1) Dabigatran 150mg 2) Adjusted dose warfarin 3) Rivaroxaban 4) Apixaban	Markov model; lifetime; 3-month	Health care	71	Hypothetical cohort NVAF patients (mean age of the RE-LY trial patients)	No project funding received
Singh, 2013[44]	Canada	1) Sequential dabigatran* (110 mg if ≥75 years + creatinine clearance 30-50 mL/min) 2) Adjusted-dose warfarin 3) Left atrial appendage occlusion	Markov micro-simulation; lifetime; 1-month	Health care	76	Consecutive AF patients with non-valvular AF presenting to outpatient oral anticoagulation clinic of academic institution	Author Andrew Micieli funded by Canadian Institute Health Research (CIHR) summer studentship
Wisloff, 2013[45]	Norway	1) Sequential dabigatran* 2) Sequential dabigatran ESC dosing (150 mg <75 years, 110 mg >75 years) 3) Dabigatran 110 mg 4) Warfarin 5) Apixaban 6) Rivaroxaban	Markov model; lifetime; 12-month	Health care	NR	Patients with AF at moderate or high levels of stroke risk	NR

Discrete Events Simulation Models							
Pink, 2011[24]	UK	1) Dabigatran 150 mg 2) Dabigatran 110 mg 3) Warfarin	Discrete event simulation (DES) model; lifetime; cycle NA	Health care	71.5	Cohorts of 50,000 simulated patients reflective of RE-LY trial; non-valvular AF at moderate to high risk of stroke (mean baseline $CHADS_2 = 2.1$)	The Medical Research Council
Pink, 2014[25]	UK	1) Dabigatran 150 mg 2) Clinical warfarin 3) Genotype-guided, dose-adjusted warfarin 4) Rivaroxaban 5) Apixaban	Discrete event simulation model; lifetime; cycle NA	Health care	72.3	Average profile of the UK AF population; for each treatment, identical cohorts of 100,000 patients were generated	The Medical Research Council
Trial-Based Economic Evaluations							
Chang, 2013[23]	Hong Kong	1) Dabigatran 2) Warfarin	Cost-effectiveness analysis; cycle NA	Hospital; Patient	70.1	244 patients from Hong Kong teaching hospital; comparator groups were matched for demographic characteristics and medical history	School of Pharmacy: The Chinese University of Hong Kong

**sequential dabigatran dosing: 150 mg for patients <80 years and 110 mg for patients >80 years.*

AF = atrial fibrillation; HF = heart failure; INR = international normalized ratio; NR = not reported; NA = not applicable; TIA = transient ischemic attack; MI = myocardial infarction; AHA = American Heart Association; VA = veterans affairs; AC =anticoagulation.

TABLE 2 Management of Warfarin INR Control

Author, Year, Country	Addressing INR monitoring	Base case TTR	Warfarin Monitoring (# INR tests; # GP visits/ year)	Dabigatran Monitoring Assumptions
Markov Models based on Sorensen, 2011				
Sorensen, 2011[22]; Canada	• comparators included 1) "trial-like" warfarin as observed in the RE-LY trial, 2) "real-world" prescribing based on retrospective Canadian study; • sensitivity analysis on degree of INR control	Trial-like: age <80: 65%, age ≥80: 64%; Real-world: 59%	NR; NR	NR
González-Juanatey, 2012[30]; Spain	• % of time above and below therapeutic range of INR maintained the original ratio of the base case: INR <2 = 15.2% when TTR = 72.6; INR <2 = 23.9% when TTR = 57.1;	64.4%	Pts with good control: 13, pts with poor control: 19.5; NR	NR
Kansal, 2012[31]; UK	• trial-like INR control • assumed TTR consistent with RE-LY • sensitivity analysis on % patients in target INR range	64%	NR; NR	NR
Langkilde, 2012[32]; Denmark	sensitivity analysis with average TTR levels achieved by study centres (4 quartiles)	64%	NR; NR	3 GP and 1 cardiologist visit in first year; 1 GP visit thereafter
Andrikopoulos, 2013[27]; Greece	warfarin/acenocoumarol dosage: 15% increase for patients with INR <2; 15% decrease if INR >3	NR	NR; NR (regular follow-up, not attributed to INR costs; 2 extra visits and tests if outside range)	NR
Bergh, 2013[28]; South Africa	base-case scenario INR adjustment: weighted warfarin approach	NR	INR within 2.0–3.0: 12; 3 specialist consultations. INR outside range: 24; 6 specialist consultations	NR
Pletscher, 2013[33]; Switzerland	sensitivity analysis: TTR 55% TTR 72%	64%	11.6 first month, 1.14 per month thereafter; 1 per INR test	1 INR test and 1 GP visit before initiation of treatment

Wouters, 2013[35]; Belgium	• `trial-like` INR control in base case • scenario analyses: 1) real-world INR control (average TTR in Belgian clinical practice: 53%) 2) treatment mix of warfarin, aspirin & no treatment	64%	18; 18	4 GP visits/year
Other Markov Models				
Freeman, 2011[39]; USA	NR	NR	14; NR	GP visits at 1 and 3 months; every 3 months in first year; every 4 months thereafter
Shah, 2011[43]; USA	TTR varied in sensitivity analysis: range 57% to 72%	NR	14; 14	not included
Davidson, 2012[38]; Sweden	TTR varied in sensitivity analysis: well-controlled pts TTR>72.6%; poorly-controlled pts TTR 57.1%-65.5%	NR	16.94; 1	1 physician visit per year
Kamel, 2012[41]; USA	TTR varied in sensitivity analysis: range 57%-73%	64%	14; NR	regular office visits for monitoring
Wells, 2012[5]; Coyle, 2013[29]; Canada	Stratified analysis: centre-specific average TTR (TTR < 66%; TTR ≥ 66%)	NR	NR; 0 (no incremental visits)	NR
You, 2012[36]; USA	• pts with wild-type CYP2C9 and VKORC1 (normal warfarin sensitivity) receive usual AC care (at least monthly monitoring); • pts with genotypes of high or low warfarin sensitivity managed by intensified AC care (monitoring at least twice/month and patient education). • sensitivity analyses: one-way: TTR 65–100% in genotype-guided AC; stroke rate when INR was in target range; two-way: variation of warfarin utility vs. TTR in genotype-guided AC	Usual AC: 64% Genotype-guided AC: 78.9%	12; NR	NR
Canestaro, 2013[37]; USA	NR	NR	5 in first month, 1 per month thereafter; 1 every 3 months	GP visits every 6 months

(*Continues*)

TABLE 2 (*Continued*)

Author, Year, Country	Addressing INR monitoring	Base case TTR	Warfarin Monitoring (# INR tests; # GP visits/ year)	Dabigatran Monitoring Assumptions
Harrington, 2013[40]; USA	INR not incorporated as a model parameter in the study	NR	NR; NR	GP visit every 3 months
Nshimyumukiza, 2013[42]; Canada	• assumed stable maintenance dose of warfarin after 1 year • TTR in each INR category (below, within & above) similar for both groups • % TTR below range (<2): 54% • % of increasing of TTR by genotype-guided dosing: 7.3% • sensitivity analysis: varied cost of genetic tests and % time in TTR	64%	NR; NR	Assumed no lab monitoring required
Rognoni, 2014[34]; Italy	sensitivity analysis: TTR varied by quartiles (%): <57.1, 57.1-65.5, 65.5-72.6, >72.6	NR	13.9; 13.9	1 GP visit per year for renal function
Singh, 2013[44]; Canada	INR monitoring not addressed. Labile INR (TTR < 60%) part of calculation for HAS-BLED score.	INR out of therapeutic range: 22.1%	NR; NR	NR
Wisloff, 2013[45]; Norway	Subgroup analyses with efficacy input according to the group with INR control closest to what is assumed for Norway (TTR ~ 70%)	NR	13; NR	4.17 GP visits per year
Discrete Event Simulation Models				
Pink, 2011[24]; UK	Subgroup analysis: centres reporting mean TTR more or less than 65.5%; and patients' TTR more or less than 66.8%	NR	NR; NR	NR
Pink, 2014[25]; UK	Pharmacokinetic-pharmacodynamic (PKPD) simulation done to predict TTR for different dosing algorithms; • sensitivity analysis: duration of benefit from genetic testing; • separate analysis to externally validate simulated INR data;	NR	NR; NR	NR
Trial-Based Economic Evaluations				
Chang, 2013[23]; Hong Kong	More follow-up clinic visits & lab tests for warfarin usage	NR	NR; NR	NR

INR = international normalized ratio; NR = not reported; pts = patients; TTR = time in therapeutic range.

using the same cost or temporal perspectives, there were considerable differences in the magnitude of costs and QALYs generated for each treatment. For example, the expected total costs with warfarin from 2 Canadian analyses[22,29] based on Markov models with a lifetime time horizon and a health care perspective differed by more than $24,000 (i.e., $18,620 CAD vs. $42,946 CAD). Two US Markov models with similar time horizon and perspectives also demonstrated substantial differences in the magnitude of total costs (see Table 2) and the QALYs generated by the model (e.g., for warfarin: 10.28 QALYs[39] compared to 5.87 total QALYs[37]).

In terms of ICER, the range was from $1,300 USD/QALY to $151,700 USD/QALY (see Table 2). Specifically, 18 studies reported ICERs less than $50,000 USD/QALY gained[5,22,24,25,27-36,38,40–42,44] and two studies, both from the USA[39,43] reported ICERs between $50,000–100,000 USD/QALY gained. Another study[45] reported ICERs which ranged from less than $50,000 USD/QALY to $103,000 USD/QALY gained, depending on the level of stroke risk and the dosing regimen indicated for dabigatran. One publication[37] reported an ICER of approximately $150,000 USD/QALY gained. Higher ICERs of the studies conducted in the USA[37,39,43] may be attributed to the comparably higher daily drug cost (approximately $9; 2–3 folds) of dabigatran.

Overall, base case cost-effectiveness results did not change by study type (e.g., Markov or DES models) or sponsor status, as the non-industry-sponsored studies[5,24,25,29,34,36,42,44] also reported favourable cost-effectiveness results for dabigatran. The overall conclusions also did not change when the base case analyses focused on incremental costs per LYG (Online Resource III) as all the studies reported ICERs less than $50,000/LYGs in the base case analyses.

Factors Influencing Cost-Effectiveness Results

Sensitivity analyses were conducted in all studies to evaluate the impact of key clinical and economic model inputs on the base case results, such as anticoagulation control, risk of stroke and bleeding events, age, and cost of anticoagulation monitoring. Few studies also included the cost of bleeding due to dabigatran in their sensitivity analyses. The following presents the conclusions of these analyses.

Time in Therapeutic Range (TTR)

Studies that evaluated TTR in sensitivity analyses[5,22,24,28–36,38,41–43,45] examined the impact of having good INR control (e.g., TTR of 72%) or poor INR control (e.g., TTR of 57%) as opposed to the base case TTR value of 64% (i.e., RE-LY) used in many models. Although TTR had a significant impact on the results (i.e., higher warfarin TTR equals higher ICERs), changing the TTR value did not impact the conclusions of the 8 studies based on the Sorensen model. For example, in an adaptation of the Sorensen model for Belgium,[35] assuming a higher TTR of 80% increased the ICER by 76% (from €2,807 to €4,942), but dabigatran remained cost effective. In contrast, other studies reported that dabigatran would not be cost effective using higher TTR values (65% to 73%) for warfarin.[29,41,43] In Canada, the ICER increased from $7,500/QALY gained when using a TTR value lower than 66% to $76,000/QALY gained when using a TTR equal or greater than 66%.[29] Conversely, 2 studies showed that the TTR must be as high as 98–99% before dabigatran was no longer considered cost effective.[35,36]

Rate of Ischemic Stroke

Similar to the results of the sensitivity analyses of anticoagulation control, no major changes to the interpretation of cost-effectiveness results were observed in the Sorensen-based models when the risk of stroke was varied. According to Kamel et al.[41] and Coyle et al,[29] the higher the risk of stroke associated with dabigatran, the greater the ICER of dabigatran relative to warfarin, resulting in ICERs that were significantly different in comparison to the base case ICER. While the ICER in Kamel et al.[41] was still cost effective, the ICER of Coyle et al.[29] was greater than $100,000/ QALY. ICERs were inversely related to the rate of stroke with warfarin in the analysis by Freeman et al,[39] with lower ICERs shown for patients at higher risk for stroke (2.35% per year with warfarin) compared to base case (1.2% risk). Three studies[39,43,45] analyzed the effect on the ICER with different combinations of stroke risk (e.g., $CHADS_2$-VASC score) and bleeding risk (e.g., HAS-BLED score). Dabigatran was found to be cost effective in most combinations except when lower stroke risk was combined with a higher bleeding risk.[39,45]

TABLE 3 Cost Utility Results for Dabigatran 150 mg versus Warfarin

Author & Year	Currency & Year of Costing	Total Costs Dabigatran 150 mg	Total Costs Warfarin	Incremental Costs	Total QALYs Dabigatran	Total QALYs Warfarin	Incremental QALYs	ICUR ($/QALY)	ICUR in USD (May 13, 2014)
Markov Models Based on Sorensen 2011									
Sorensen, 2011[22]	2010 $ (CAD)	sequential: 45,124	trial-like: 42,946 real-world: 44,020	2,178 1,104	7.29	7.08 7.01	0.21 0.28	10,440 3,962	10,660 4,045
Gonzàlez-Juanatey, 2012[30]	2010 € (Euro)	sequential: 15,193	10,343	4,851	8.73	8.45	0.28	17,581	26,807
Kansal, 2012[31]	2010 £ (GBP)	start at <80: 19,645 start at ≥80: 10,424	18,474 9,919	1,171 505	8.06 4.11	7.82 4.04	0.24 0.07	4,831 7,090	9,046 13,277
Langkilde, 2012[32]	2011 € (Euro)	sequential: 18,752	16,886	1,866	8.59	8.32	0.27	6,950	10,284
Andrikopoulos, 2013[27]	2012 € (Euro)	34,836	30,618	4,218	10.01	9.64	0.37	11,400	16,273
Bergh, 2013[28]	2011 R (ZAR)	sequential: 320,286	trial-like: 301,249	19,037	7.19	6.98	0.21	93,290	9,753
Pletscher, 2013[33]	2008 SwF (CHF)	150 mg: NR sequential: NR	NR	2,360 2,907	NR	NR	0.24 0.28	9,702 10,215	12,945 13,629
Wouters, 2013[35]	2012 € (Euro)	sequential: 13,333	trial-like: 12,454 real-world: 12,864	879 469	9.51	9.19 9.02	0.32 0.49	2,807 970	4,006 1,383
Other Markov Models									
Freeman, 2011[39]	2008 $ (USD)	168,398	143,193	25,205	10.84	10.28	0.56	45,372	53,841
Shah, 2011[43]	2010 $ (USD)	43,700	23,000	20,700	8.65	8.4	0.25	82,800	92,090
Davidson, 2012[38]	2010 € (Euro) (€1=SEK 9)	sequential: 27,009	24,797	2,212	8.6	8.31	0.29	7,742	11,805
Kamel, 2012[41]	2010 $ (USD)	NR	NR	9,000	4.27	3.91	0.36	25,000	27,805

Wells, 2012[5]; Coyle, 2013[29]†	2011 $ (CAD)	21,420	18,620	2,800	6.63	6.48	0.15	17,525	17,366
You, 2012[36]*	2012 $ (USD)	92,684	genotype-guided: 85,627 usual AC: 90,481	7,057 2,203	10.06	9.55 9.44	0.51 0.62	13,810 3,547	14,379 3,693
Canestaro, 2013[37]	2011 $ (USD)	88,994	49,638	39,356	6.15	5.87	0.28	140,557	151,710
Harrington, 2013[40]	2012 $ (USD)	82,719	77,813	4,906	8.41	7.97	0.44	11,150	11,609
Nshimyu-mukiza, 2013[42]	2011 $ CAD	8,494	genetic-guided: 7,749 standard dosing: 7,289	745 1,205	3.78	3.54 3.53	0.24 0.25	3,048 4,764	3,020 4,720
Rognoni, 2014[34]	2013 € (Euro)	$CHADS_2 \leq 1$: 22,122 $CHADS_2 = 2$: 19,065 $CHADS_2 \geq 3$: 18,813	14,138 12,801 14,115	7,984 6,264 4,698	12.22 9.58 7.51	11.13 8.76 7.12	1.09 0.82 0.39	7,324 7,611 12,015	10,116 10,512 16,596
Singh, 2013[44]	2012 $ (CAD)	25,760	21,429	4,331	4.64	4.55	0.09	48,122	46,001
Wisloff, 2013[45]§	2012 kr (NOK)	<u>Medium stroke risk</u> NoMA: 497,467 ESC: 517,394	458,510	38,957 58,884	9.24 9.22	9.12	0.12 0.10	324,641 588,840	57,039 103,459
		<u>High stroke risk</u> NoMA: 567,702 ESC: 589,909	548,698	19,004 41,211	8.43 8.41	8.25	0.18 0.16	106,142 257,568	18,648 45,254

(*Continues*)

TABLE 3 (*Continued*)

Author & Year	Currency & Year of Costing	Total Costs Dabigatran 150 mg	Total Costs Warfarin	Incremental Costs	Total QALYs Dabigatran	Total QALYs Warfarin	Incremental QALYs	ICUR ($/QALY)	ICUR in USD (May 13, 2014)
Discrete Event Simulation Models									
Pink, 2011[24]‡	2009 £ (GBP)	150 mg: 9,850 sequential: 9,912	6,480	3,370 3,432	6.57 6.53	6.39	0.15 0.14	23,082 24,340	44,701 47,137
Pink, 2014[25]	2011 £ (GBP)	8,426	genotype-guided: 5,921 clinical: 5,880	2,505 2,546	5.82	5.72 5.72	0.10 0.10	24,320 24,018	44,199 43,650

** NR = not reported.*

† Differences in ICUR reported in Wells 2012 and Coyle 2013

‡ Pink 2011: sequential dabigatran dosing (110 mg bid for patients ≥ 80 years) based on post-hoc subgroup analysis; year of costing for dabigatran is NR.

§ Wisloff 2013: NoMA - Norwegian Medicines Agency dabigatran dosing of 2 × 150 mg up to 80 years and 2 × 110 mg thereafter; ESC - European Society of Cardiology dabigatran dosing of 2 × 150 mg up to 75 years and 2 × 110 mg thereafter; medium stroke risk= CHA2DS2-VASc = 1 and HAS-BLED=0; high stroke risk: CHA2DS2-VASc = 2 and HAS-BLED=1.

** You, 2012: AC = anticoagulation care.*

Bleeding Rates

With respect to bleeding rates, no impact on the overall cost-effectiveness conclusions was observed in the studies when varying rates of ICH, HS, or GI bleeds.[24,31,35,37,49,40,42,43] Two studies incorporated the cost of bleeding due to dabigatran in their sensitivity analyses. When the cost of bleeding was increased by 20% the observed influence on the ICER was minimally incremental (€1,866 to €2,016).[32] Similarly, there was no influence on the reported ICER; however, the associated cost due to bleeding or the bleed rates were not explicitly stated.[24] For example, the observed change was €6950/QALY to €7510/QALY in the publication by Langkilde et al.[32] whereas the ICER remained between £20,000 and £30,000 in the analysis conducted by Pink et al.[24]

Age

The effect of age on the cost effectiveness of dabigatran was primarily assessed in sensitivity analysis[5,24,25,27,29–31,34,35,37,39,41,43,45] based on using a lower 110 mg dose for those aged 80 and over (i.e., sequential dosing) or using higher rates of stroke and bleeding associated with higher age. With the exception of one study,[41] increasing age did not change the cost-effectiveness results. However, in the economic evaluation by Kamel et al,[41] when patients were stratified according to age, 150 mg of dabigatran twice daily was cost effective when treatment was initiated before age 81, but the increased background risk of mortality above this age led to unfavourable cost-effectiveness results with the same dose regimen.

Costs of INR Monitoring

When the costs associated with INR monitoring of warfarin therapy were varied in sensitivity analyses,[5,22,24,28–33,35,37] as expected, higher warfarin monitoring costs resulted in lower ICERs for dabigatran compared to warfarin therapy. Two studies showed that dabigatran became the dominant treatment (i.e., less costly and more effective) when the annual cost of INR monitoring was increased to €744[32] or €1037.[35] In addition, several studies that included management costs for both warfarin and dabigatran found that dabigatran was still cost effective.[32–35,38,41]

Other Sensitivity Analyses

Other factors less commonly explored which may have had an impact on the results included different utility values for the health states considered in the models (e.g., disutility following stroke), drug costs, long-term costs of stroke, discount rates, and time horizon. As demonstrated by Pink et al,[25] the ICER was sensitive to vascular death rates and duration of treatment benefits, however dabigatran remained cost effective. Results were robust to the variation in time horizon in Shah et al.,[43] but had a significant impact in 4 other studies.[5,22,29,30,35] Kansal et al,[31] and Sorensen et al,[22] reported that the cost of long-term follow-up care for disabled patients influenced the cost effectiveness whereas the discount rates appeared to have had no influence in the results of few other studies.[27,31,32,38] In a 3-way sensitivity analyses, Shah et al., demonstrated that dabigatran was only cost effective in patients with moderate risk of stroke (i.e., $CHADS_2 = 2$) if they had a high risk of major bleeding (>6% per year) and had poor INR control with warfarin.[43] The impact of simultaneously varying all input parameters using Monte Carlo simulations were explored in 19 studies[5,22,24,25,27,29–31,33–42,44,45] to address parameter uncertainties. These probabilistic sensitivity analyses confirmed the base case results.

DISCUSSION

We identified 23 economic evaluations comparing dabigatran versus warfarin for the prevention of stroke in patients with AF. Review of the base case analyses indicates that dabigatran is a cost-effective alternative to warfarin therapy for these patients according to commonly cited thresholds.[20,21] However, as shown in this review, there are many factors which can influence the cost-effectiveness results. The quality of anticoagulation control with warfarin, in terms of the TTR, was shown to be an important factor in estimating the relative cost effectiveness of dabigatran. Although most studies assumed a TTR of 64%, based on the RE-LY trial, sensitivity analyses using higher TTRs resulted in higher ICERs for dabigatran versus warfarin. While changing the TTR values did not impact the cost effectiveness results of many studies, 2 studies demonstrated less favourable cost-effectiveness results with higher TTR (i.e., 65% or 73%).[29,41]

This demonstrates the importance of understanding TTR in real-world settings and using this TTR value in the base case cost-effectiveness analyses. For example, the mean TTR is greater than 70% in many countries including Canada, Australia and the Scandinavian countries.[46] The higher TTR reflects superior overall warfarin management, which may then decrease the cost effectiveness of dabigatran in these settings.[46] For example, subgroup analyses of RE-LY have shown that the risk of stroke was similar between dabigatran and warfarin with a TTR greater than 72.6%[46]. The risk of stroke and bleeding also influenced the actual cost-effectiveness ratios of dabigatran compared to warfarin, however, as demonstrated by the results of the sensitivity analyses, there were no changes to the overall conclusions regarding the cost effectiveness. However, none of these studies used real-world data for modelling dabigatran bleeding and management or stroke reduction. In particular, it is currently unknown how the conclusions of these sensitivity analyses would have changed if the base case analyses used a higher TTR (e.g., 71%) value instead of using the TTR value from RE-LY (e.g., 64%).

Several limitations were associated with this review. First, with no access to the models or associated technical reports, it was not possible to fully appraise these studies or explain the differences between studies. Publication space limits often prohibit full description of the nuances of models or a full description of all the clinical and economic assumptions. Second, many economic models often do not follow standard reporting guidelines for economic evaluations[47] which limits the transparency and clarity of each study's findings. Furthermore, due to the primary objective of identifying factors influencing the cost-effectiveness results, we did not evaluate the studies against some check lists for economic evaluations.[47,48] In this review, we noted inconsistencies in the reporting of the clinical outcomes and costs which made comparisons between studies and across countries difficult. Additionally, there is always a risk that a particular relevant study was missed, but this risk was minimized by hand searching the references and checking with other reviews. Finally, our study was only looking at dabigatran and ignored other NOACs. Although we did not evaluate the other NOACs, we believe that our observations also apply to the factors influencing the cost-effectiveness of these agents. As a reference, the recent review by Fereira et al.,[12] identified 3 models for apixaban and 2 for rivaroxaban compared to 18 for dabigatran (as opposed to 23 in our study).

Despite these limitations, this review of the key factors influencing the cost-effectiveness results of 23 economic evaluations of dabigatran has highlighted that most of our current knowledge on the economic value of dabigatran is based on randomized controlled clinical trial evidence. With new real-world data becoming available, there is opportunity to re-evaluate the cost-effectiveness of dabigatran versus warfarin. A recent study[49] using a large cohort of elderly Medicare individuals with non-valvular AF confirmed that when compared to warfarin, dabigatran was statistically associated with reduced risk of stroke, ICH, and mortality but increased the risk of major GI bleeding. As new effectiveness data become available, future research is warranted to re-evaluate the cost-effectiveness of dabigatran in real-life conditions.

CONCLUSION

Overall, the economic analyses published find dabigatran to be a cost-effective option compared to warfarin for the prevention of stroke in AF patients. However, there are several underlying factors leading to variability in the economic analyses, even though they are primarily based on the results of a single, large, multinational RCT. Economic evaluations using real-world data on the relative clinical efficacy and safety, costs of bleeding due to dabigatran, treatment compliance or discontinuations over time, jurisdiction-specific data on INR control and monitoring costs, should be conducted.

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