Rev Port Cardiol. 2015;34(3):179–191

Revista Portuguesa de Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

ORIGINAL ARTICLE

Systematic review of cost-effectiveness analyses of novel oral anticoagulants for stroke prevention in atrial fibrillation☆

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Received 11 July 2014; accepted 16 August 2014
Available online 27 February 2015

KEYWORDS
Novel oral anticoagulants;
Apixaban;
Dabigatran;
Edoxaban;
Rivaroxaban;
Cost-effectiveness;
Atrial fibrillation

Abstract
Introduction and Objectives: Novel oral anticoagulants are emerging options for the prevention and treatment of thromboembolic diseases. They are increasingly used in clinical practice due to their simplicity of use and clinical benefits, but an important step is to evaluate their cost-effectiveness. The aim of the AFFORD study (A Review of Cost EFFectiveness of Novel ORal Anticoagulant Drugs) was to perform a systematic review of cost-effectiveness studies of novel oral anticoagulants for stroke prevention in non-valvular atrial fibrillation (AF).
Methods: A systematic review of the literature was conducted by searching the PubMed, Embase, Scopus, Cochrane and Web of Knowledge databases to identify all cost-effectiveness studies of novel oral anticoagulants for stroke prevention in AF.
Results: The search identified 27 studies, 18 with dabigatran, three with apixaban, two with rivaroxaban and four with at least two of these drugs. The incremental cost-effectiveness ratios were 30 405±16 101 euros per quality-adjusted life-year (QALY) for dabigatran 110 mg, 17 566±16 902 euros/QALY for dabigatran 150 mg, 8102±3252 euros/QALY for age-adjusted dabigatran, 11 897±3341 euros/QALY for apixaban and 17 960±12 005 euros/QALY for rivaroxaban.
Conclusion: The present systematic review demonstrates that novel oral anticoagulants are cost-effective for stroke prevention in AF.

☆ Please cite this article as: Ferreira J, Mirco A. Revisão sistemática das análises custo-efetividade dos novos anticoagulantes orais na prevenção do acidente vascular cerebral na fibrilhação auricular: estudo AFFORD. Rev Port Cardiol. 2015;34:179–191.

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PALAVRAS-CHAVE
Novos anticoagulantes orais;
Apixabano;
Dabigatrano;
Edoxabano;
Rivaroxabano;
Custo-efetividade;
Fibrilhação auricular

Revisão sistemática das análises custo-efetividade dos novos anticoagulantes orais na prevenção do acidente vascular cerebral na fibrilhação auricular: estudo AFFORD

Resumo
Introdução e objetivos: Os novos anticoagulantes orais são opções emergentes para a prevenção e tratamento das doenças tromboembólicas. São cada vez mais usados na prática clínica pela facilidade do seu uso e pelos seus benefícios clínicos, mas a sua utilização mais generalizada carece de demonstração de custo-efetividade. O objetivo do estudo A Review of Cost EFFectiveness of Novel ORal Anticoagulant Drugs (AFFORD) consistiu na realização de uma revisão sistemática dos estudos de custo-efetividade dos novos anticoagulantes orais na prevenção do acidente vascular cerebral (AVC) na fibrilhação auricular não valvular (FA).
Métodos: Foi realizada uma revisão sistemática da literatura nas bases de dados Pubmed, Embase, Scopus, Cochrane e Web of Knowledge para identificar todos os estudos de custo-efetividade dos novos anticoagulantes orais na prevenção do AVC na FA.
Resultados: A pesquisa selecionou 27 estudos, 18 com dabigatrano, três com apixabano, dois com rivaroxabano e quatro com pelo menos dois destes fármacos. Os rácios custo-efetividade incremental por anos de vida ajustados para qualidade foram de 30.405 ± 16.101 euros para o dabigatrano 110 mg, 17.566 ± 16.902 euros para o dabigatrano 150 mg, 8.102 ± 3.252 euros para o dabigatrano ajustado à idade, 11.897 ± 3.341 euros para o apixabano e 17.960 ± 12.005 euros para o rivaroxabano.
Conclusões: A presente revisão sistemática demonstra que os novos anticoagulantes orais são custo-efetivos para a prevenção do AVC na FA.

List of abbreviations

AF	atrial fibrillation
CAD	Canadian dollar
CHF	Swiss franc
EUR	euro
GBP	UK pound
ICER	incremental cost-effectiveness ratio
INR	international normalized ratio
OAC	oral anticoagulants
QALY	quality-adjusted life years
USD	US dollar
VKA	vitamin K antagonists
WTPT	willingness-to-pay threshold
ZAR	South African rand

Introduction

Health expenditure is growing faster than wealth creation in most developed countries. In Portugal, per capita state health expenditure rose from 0.3 euros in 1972 to 989.4 euros in 2012, while total expenditure increased from 2.8 million euros (0.2% of gross domestic product) in 1972 to 10 430.5 million euros (6.3%) in 2012.[1] State expenditure on drugs, which in 2010 accounted for 17% of total health spending, has risen in parallel with overall health expenditure.[1]

This investment has led to improvements in health indicators, notably increased life expectancy.[2] However, there is growing awareness that the available resources for medical treatments, including drug therapy, are increasingly limited. Economic evaluations are designed to rationalize the use of these resources and to direct them where they are most needed.

In this context, cost-effectiveness analyses are a valuable tool to compare the cost of a health intervention with the expected health gains.[3] Interventions include any action intended to improve health that uses financial and/or human resources.

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice,[4] and results in a considerable burden in economic terms as well as in morbidity and mortality. Stroke prevention by anticoagulant therapy is the mainstay of AF treatment.[5]

AF is associated with a prothrombotic state caused by atrial blood stasis and structural heart disease, which predispose to thrombus formation, particularly in the left atrial appendage, and to cardiac embolism. As a result, AF patients have a fivefold greater risk of stroke and systemic embolism than those without AF.[5]

Anticoagulant therapy is the cornerstone of prevention and treatment of thromboembolic disease.[6] Novel oral anticoagulants (OAC) represent a step forward, being easier to use and presenting a more favorable pharmacological profile than vitamin K antagonists (VKA). They also have more rapid onset of action and a more predictable anticoagulant response, eliminating the need for monitoring.[6]

Phase III clinical trials on four of the novel OAC for stroke prevention in patients with non-valvular AF revealed similar or lower rates of thromboembolism, major bleeding and adverse effects compared to warfarin or aspirin.[7–12]

Wider use of these new agents could significantly increase the number of adequately anticoagulated patients, since many AF patients do not currently receive any treatment, due to the inconvenience and drawbacks of VKA.[4,5]

However, without regular monitoring of coagulation levels, larger observational studies are needed to determine the long-term efficacy and safety of the novel OAC in patients with multiple comorbidities and under multiple medication.[6] The lack of antidotes, reliable laboratory tests and evidence of safety in real-world clinical practice, together with their high cost, have been identified as important limitations to the wider use of these new agents.

A Review of Cost EFFectiveness of Novel ORal Anticoagulant Drugs (the AFFORD study) is a systematic review of cost-effectiveness studies of novel oral anticoagulants for stroke prevention in AF, and describes their key findings.

Methods

Identification of studies

Studies that fulfilled the aims of the review were identified using a single search term, ''[(adults AND humans) AND (''new oral anticoagulants'' OR ''new oral anticoagulation'' OR ''novel oral anticoagulants'' OR ''novel oral anticoagulation'' OR ''newer oral anticoagulants'' OR ''newest oral anticoagulants'' OR ''new generation oral anticoagulants'' OR ''oral direct thrombin inhibitor*'' OR ''new oral thrombin inhibitor*'' OR ''oral factor Xa inhibitor*'' OR ''orally active factor Xa inhibitor'' OR ''orally active thrombin inhibitor'' OR rivaroxaban* OR dabigatran* OR apixaban* OR edoxaban*) AND (''cost-effectiveness analysis'' OR ''cost-effectiveness study'' OR ''cost-effective'' OR ''cost-effectiveness'') AND (''atrial fibrillation)]'', in five medical databases: PubMed, Embase, Scopus, Cochrane and Web of Knowledge.

This search identified 533 studies (Figure 1), the abstracts and articles of which were reviewed to select those performed in adult populations comparing new and conventional anticoagulants in terms of cost-effectiveness. Of these, 414 were excluded because they did not meet the required conditions and 52 because they were published as abstracts only.

After elimination of duplicates a total of 23 studies were selected.

A further four studies were selected that did not appear in the results for the above search term; three were in the reference lists of the studies analyzed and one was found in previous searches of PubMed.

Data collection

Data related to the pharmacoeconomic model included (1) country; (2) primary comparisons (the new OAC under study, dosages, comparator and daily costs); (3) model structure and assumptions including similarity to 'progenitor' models and study perspective; and (4) results including incremental costs, quality-adjusted life years (QALY), incremental cost-effectiveness ratios (ICER), willingness-to-pay thresholds (WTPT) per life-year or QALY, and sensitivity analyses.

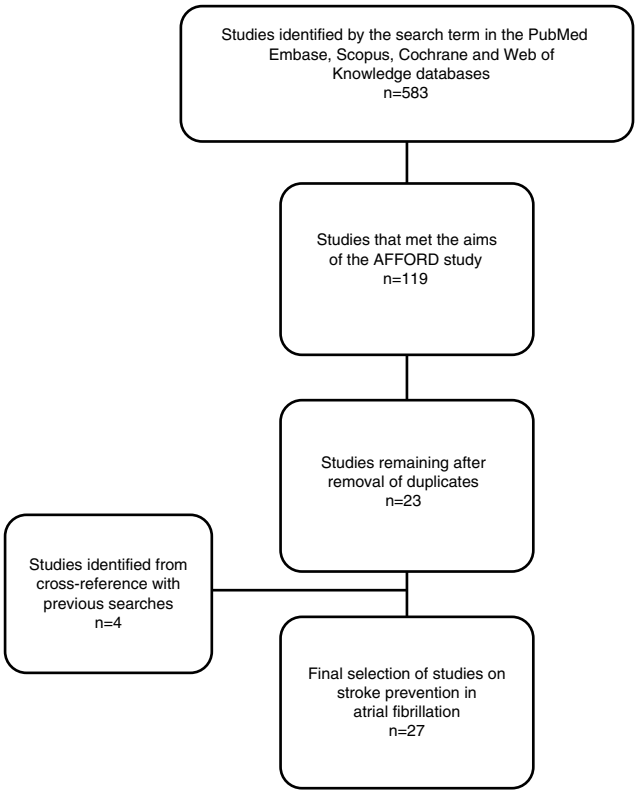

Figure 1 Selection of studies.

Evaluation of quality of studies

The quality of the studies was evaluated by the investigators on the basis of the inclusion of predefined data on the study models as specified in the criteria of the Quality of Health Economic Studies instrument.[13]

Statistical analysis

The descriptive nature of this review does not lend itself to formal statistical analysis. The characteristics and results of the pharmacoeconomic models selected were presented qualitatively, supported by figures for incremental costs, QALY, ICER, WTPT and percentages from sensitivity analyses.

Means and standard deviations of ICER in euros per QALY were calculated for each drug after currency conversion when necessary, using the exchange rates on May 16, 2014: 1 US dollar (USD)=0.7321 euros; 1 Canadian dollar (CAD)=0.6736 euros; 1 UK pound=1.2267 euros; 1 Swiss franc (CHF)=0.819 euros; 1 South African rand (ZAR)=0.0708 euros.

Results

Of the 27 studies selected (Table 1),[14–40] most were European (n=11)[15,18,19,21,22,24,26–29,33] or American (n=10).[14,16,20,31,32,34–36,38,39] Three were Canadian,[17,27,37] two Chinese[23,30] and one South African.[25]

Table 1 Characteristics and results of cost-effectiveness studies of novel oral anticoagulants for stroke prevention in atrial fibrillation.

Study	Country	New OAC	Price of new OAC	Comparator	Price of comparator	Perspective	Model	Results	WTPT and sensitivity analysis
Freeman et al.[14]	USA	Dabigatran 110 mg	USD 8	Warfarin	USD 1.07	Health system	Markov	ICER: USD 45 372/QALY	50 000 USD/QALY Dabigatran cost-effective in 80% of simulations
		Dabigatran 150 mg	USD 8					ICER: USD 51 229/QALY	Dabigatran cost-effective in 80% of simulations
Kansal et al.[15]	UK	Age-adjusted dabigatran[a]	GBP 2.52	Warfarin	GBP 0.04	Health system	Markov	ICER: GBP 4831/QALY – age <80 ICER: GBP 7090/QALY – age ≥80	GBP 20 000/QALY Probability of dabigatran being the most cost-effective: age <80: 98% age ≥80: 63%
Shah et al.[16]	USA	Dabigatran 110 mg	USD 8.88	Warfarin	USD 0.49	Health system	Markov	Incremental cost: USD 21 300 ICER: USD 150 000/QALY	USD 50 000/QALY Dabigatran 110 mg is not cost-effective
		Dabigatran 150 mg	USD 8.88					Incremental cost: USD 20 700 ICER: USD 86 000/QALY	Dabigatran 150 mg is cost-effective
Sorenssen et al.[17]	Canada	Age-adjusted dabigatran[a]	CAD 3.2	Warfarin	CAD 0.6	Health system	Markov	Incremental cost: CAD 2178 ICER: CAD 10 440/QALY	CAD 30 000/QALY Dabigatran cost-effective in 82% of simulations
		Dabigatran 110 mg	CAD 3.2					Incremental cost: CAD 4210 ICER: CAD 29 994/QALY	Dabigatran cost-effective in 42% of simulations

Table 1 (*Continued*)

Study	Country	New OAC	Price of new OAC	Comparator	Price of comparator	Perspective	Model	Results	WTPT and sensitivity analysis
		Dabigatran 150 mg	CAD 3.2					Incremental cost: CAD 1655 ICER: USD 9041/QALY	Dabigatran cost-effective in 81% of simulations
Pink et al.[18]	UK	Dabigatran 110 mg	GBP 2.52	Warfarin	GBP 0.11	-	Event simulation model	ICER: GBP 43 074/QALY	GBP 20 000/QALY Dabigatran 150 mg dominant vs. 110 mg in 76% of simulations
		Dabigatran 150 mg						ICER: GBP 23 082/QALY	Dabigatran 150 mg dominant vs. warfarin in 94% of simulations
Juanatey et al.[19]	Spain	Dabigatran 150 mg	EUR 3.03	Warfarin	EUR 0.05	Health system	Markov	Incremental cost: EUR 4851 ICER: EUR 17 581/QALY	EUR 30 000/QALY Dabigatran dominant: 96.4% of simulations
Adcock et al.[20]	USA	Dabigatran 150 mg	USD 8	Warfarin	ND	Societal	Markov	ICER: USD 12 286/QALY	USD 50 000/QALY Dabigatran dominant for daily cost <USD 13
Langkilde et al.[21]	Denmark	Age-adjusted dabigatran[a]	EUR 2.63	Warfarin	EUR 0.26	Health system	Markov	Incremental cost: EUR 1866 ICER: EUR 6950/QALY	EUR 30 000/QALY Dabigatran is cost-effective

Table 1 (*Continued*)

Study	Country	New OAC	Price of new OAC	Comparator	Price of comparator	Perspective	Model	Results	WTPT and sensitivity analysis
Ali et al.[22]	UK	Dabigatran 110 mg and 150 mg	GBP 2.4	Warfarin	GBP 0.08	ND	Prospective observational study	Cost of OAC to prevent 1 stroke/year: warfarin GBP 6219; dabigatran 110 mg GBP 28 086.5 and dabigatran 150 mg GBP 25 181	ND
You et al.[23]	China	Dabigatran 110 mg	USD 8	Warfarin	USD 1	Payer	Markov	Incremental cost: USD 16 909 ICER: dominated by dabigatran 150 mg	U SD 50 000/QALY Dabigatran cost-effective in 1.6% of simulations
		Dabigatran 150 mg	USD 8					Incremental cost: USD 7057 ICER: USD 13 810/QALY	Dabigatran cost-effective in 50.6% of simulations
Wouters et al.[24]	Belgium	Dabigatran 150 mg	EUR 2.68	Warfarin	EUR 0.32	Health system	Markov	Incremental cost: EUR 879 ICER: EUR 2807/QALY	EUR 20 000/QALY Dabigatran cost-effective in 99.85% of simulations
Bergh et al.[25]	South Africa	Age-adjusted dabigatran[a]	ZAR 24.66	Warfarin	ZAR 1.2	Payer	Markov	Incremental cost: ZAR 19 037 ICER: ZAR 93 290/QALY	ND
Davidson et al.[26]	Sweden	Age-adjusted dabigatran[a]	EUR 2.82	Warfarin	EUR 2.12	Societal	Markov	Incremental cost: EUR 2212 ICER: EUR 7742/QALY	EUR 50 000/QALY Dabigatran is cost-effective

Table 1 (*Continued*)

Study	Country	New OAC	Price of new OAC	Comparator	Price of comparator	Perspective	Model	Results	WTPT and sensitivity analysis
Pletscher et al.[27]	Switzerland	Dabigatran 110 mg	CHF 4	Phenprocoumon 2.25 mg	CHF 0.21	Payer	Markov	ICER: CHF 25 108/QALY	CHF 50 000/QALY Probability of dabigatran being the most cost-effective: 84%
		Dabigatran 150 mg	CHF 4					ICER: CHF 9702/QALY	Probability of dabigatran being the most cost-effective: 95.8%
		Age-adjusted dabigatran[a]	CHF 4					ICER: CHF 10 215/QALY	Probability of dabigatran being the most cost-effective: 97.7%
Andrikopoulos et al.[28]	Greece	Dabigatran 110 mg	EUR 2.72	Warfarin	EUR 0.04	Payer	Markov	Incremental cost: EUR 4996 ICER: EUR 16 653/QALY	
		Dabigatran 150 mg	EUR 2.72					Incremental cost: EUR 4218 ICER: EUR 11 400/QA LY	EUR 50 000/QALY Dabigatran 150 mg cost-effective in 87% of simulations
Miguel et al.[29]	Portugal	Age-adjusted dabigatran[a]	EUR 2.53	Warfarin	EUR 0.08	Societal	Markov	Incremental cost: EUR 2978 ICER: EUR 8409/QALY	EUR 30 000/QALY Dabigatran is cost-effective
Chang et al.[30]	China	Dabigatran	USD 2.3 to USD 2.5	Warfarin	USD 1.3	Payer	Markov	ICER: USD 68 333/event prevented	ND

Table 1 (*Continued*)

Study	Country	New OAC	Price of new OAC	Comparator	Price of comparator	Perspective	Model	Results	WTPT and sensitivity analysis
		Dabigatran	USD 1.7	Warfarin	USD 0.03 to USD 0.04			ICER: Dabigatran dominant (cost reduction: USD 34 350/event prevented)	
Kamel et al.[31]	USA	Dabigatran 150 mg	USD 6.75	Warfarin	USD 1.04	ND	Markov	Incremental cost: USD 9000 ICER: USD 25 000/QALY	USD 50 000/QALY Dabigatran cost-effective in 87% of simulations
Lee et al.[32]	USA	Rivaroxaban	USD 6.8	Warfarin	USD 1.06	Payer/health system	Markov	Incremental cost: USD 5912 IICER: USD 27 498/QALY	USD 50 000/QALY Rivaroxaban cost-effective in 80.1% of simulations
Kleintjens et al.[33]	Belgium	Rivaroxaban	EUR 2.70	–	EUR 0.31	Payer	Markov	Incremental cost: EUR 828 ICER: EUR 8809/QALY	EUR 35 000/QALY Rivaroxaban cost-effective in 87% of simulations
Lee et al.[34]	USA	Apixaban	USD 6.8	Aspirin	USD 0.02	Health system	Markov	Incremental cost: USD 9151 IICER: USD 16 205/QALY	USD 50 000/QALY Apixaban cost-effective in 87.5% of simulations
Lee et al.[35]	USA	Apixaban	USD 6.87	Warfarin	USD 0.2	Health system	Markov	Cost reduction: USD 8934	USD 50 000/QALY Apixaban cost-effective in 80.1% of simulations
Kamel et al.[36]	USA	Apixaban	USD 7	Warfarin	ND	Societal	Markov	Incremental cost: USD 3200 ICER: USD 11 400/QA LY	USD 50 000/QALY Apixaban cost-effective in 62% of simulations
Coyle et al.[37]	Canada	Dabigatran 110 mg	ND	Warfarin	ND	Payer	Markov + meta-analysis	Incremental cost: CAD 4184 ICER: CAD 66 354/QALY	CAD 50 000/QALY Dabigatran cost-effective in 1.6% of simulations

Table 1 (*Continued*)

Study	Country	New OAC	Price of new OAC	Comparator	Price of comparator	Perspective	Model	Results	WTPT and sensitivity analysis
		Dabigatran 150 mg						Incremental cost: CAD 2866 ICER: CAD 20 797/QALY	Dabigatran cost-effective in 50.8% of simulations
		Rivaroxaban						Incremental cost: CAD 3396 ICER: CAD 55 757/QALY	Rivaroxaban cost-effective in 2.1% of simulations
		Apixaban						Incremental cost: CAD 3346 ICER: CAD 24 312/QALY	Apixaban cost-effective in 44.1% of simulations
Harrington et al.[38]	USA	Dabigatran 150 mg	USD 7.3	Warfarin	USD 0.35	Societal	Markov	Incremental cost: USD 4906 ICER: 3190 USD/QALY	USD 50 000/QALY Dabigatran cost-effective in 40% of simulations
		Rivaroxaban	USD 7.29					Incremental cost: USD 925 ICER: USD 11 150/QALY	Rivaroxaban cost-effective in 14.9% of simulations
		Apixaban	USD 10.34					Incremental cost: USD 7513 ICER: USD 15 026/QALY	Apixaban cost-effective in 45.1% of simulations
Deitelzweig et al.[39]	USA	Dabigatran 150 mg	ND	Warfarin	ND	Payer	Markov	Cost reduction: USD 179	ND
		Rivaroxaban 10 mg						Cost reduction: USD 89	ND
		Apixaban 5 mg						Cost reduction: USD 485	ND
Kansal et al.[40]	Canada	Age-adjusted dabigatran[a]	ND	Warfarin	ND	Payer	Markov	Incremental cost: CAD 1579/patient ICER: CAD 6889/QALY	CAD 30 000/QALY
		Rivaroxaban	ND					Incremental cost: CAD 1732/patient ICER: CAD 22 475/QALY	

[a] Subgroup of patients aged <75 or with moderate renal failure (creatinine clearance ≥30 ml/min and <50 ml/min).
ND: no data.

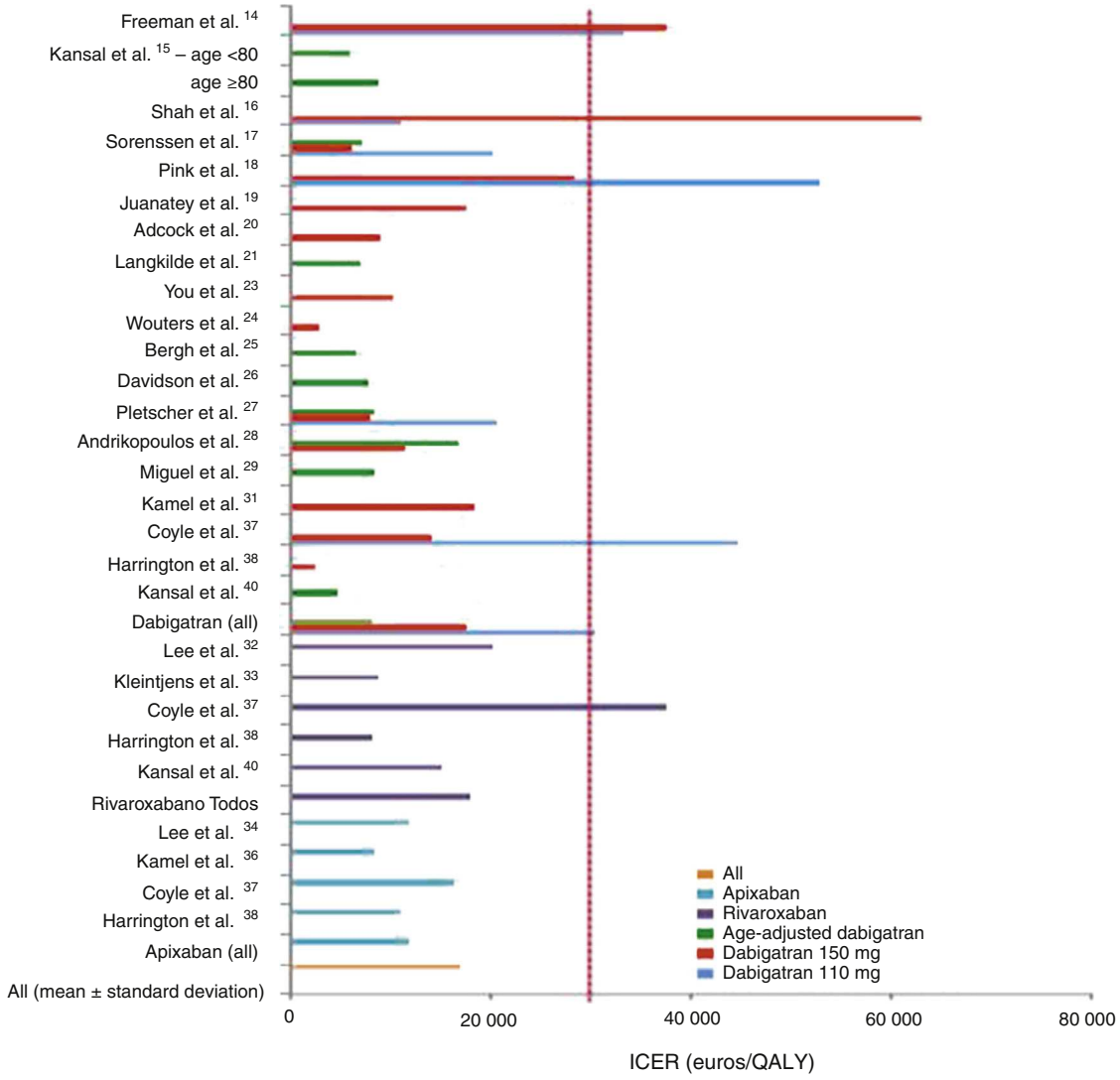

Figure 2 Graphical representation of the results of the AFFORD study, showing incremental cost-effectiveness ratios (ICER) in euros per quality-adjusted life year (QALY) after currency conversion when necessary. The vertical line represents the willingness-to-pay threshold of 30 000 euros per QALY adopted in Portugal.

The most frequent study perspectives were the health system (n=11),[14–17,19,21,24,26,29,33,35] the payer (n=9)[23,25–27,30,33,37,39,40] and societal (n=3).[20,36,38]

A Markov model was used in most studies (93%),[14–17,19–21,23–40] while one used a discrete event simulation model[18] and one was a prospective observational study.[22]

Dabigatran was the subject of most of the selected studies (67%).[14–31] Apixaban was evaluated in three studies[34–36] and rivaroxaban in two.[32,33] All the others compared at least two of the new OAC with warfarin.[37–40]

The most commonly used comparator was adjusted-dose warfarin, and variability in international normalized ratio (INR) control was taken into account in most studies. The only studies not to use warfarin as comparator were Pletscher et al.[27] (who used phenprocoumon, the most common VKA in Switzerland, where the study was carried out), and Lee et al.[34] (whose study was based on the results of the AVERROES trial[10] comparing apixaban with aspirin in AF patients unsuitable for warfarin).

In general, all the studies indicated that the new OAC were cost-effective, with ICERs below the WTPT. The latter was set by the authors but was mainly in agreement with those set by individual national health systems for purposes of reimbursement. Mean ICERs were 30 405±16 101 euros/QALY for dabigatran 110 mg, 17 566±16 902 euros/QALY for dabigatran 150 mg, 8102±3252 euros/QALY for age-adjusted dabigatran, 11 897±3341 euros/QALY for apixaban and 17 960±12 005 euros/QALY for rivaroxaban (Figure 2).

In studies on dabigatran only, the 150 mg dose tended to be more cost-effective, although there was some variation in sensitivity analyses. Age-adjusted dabigatran (150 mg twice daily for patients aged <80 years and 110 mg twice daily for those aged ≥80 years) was also cost-effective in all the studies in which it was analyzed.[15,17,21,25–27,29,40] The 110 mg

dose, as well as generally having a higher incremental cost, was not cost-effective in 43% of the models that analyzed it separately.[16,23,37]

The review also included an economic evaluation carried out in Portugal analyzing the cost-effectiveness of dabigatran for stroke prevention in patients with AF, which included in its analysis both economic data and treatment costs. The clear conclusion was that dabigatran is cost-effective in clinical practice in Portugal.[29]

The two studies on rivaroxaban, one American[32] and the other Belgian,[33] both showed that this agent was cost-effective in most simulations in sensitivity analyses.

Of the three studies on apixaban, all carried out in the USA, this agent was associated with savings in a model comparing it with aspirin over 10 years[35] and another using warfarin as comparator.[35] In the third study, apixaban was cost-effective in 62% of simulations in sensitivity analysis.[36]

Results of studies comparing all three new OAC[37–39] indicate that apixaban is the most cost-effective, followed by dabigatran and rivaroxaban. In Coyle et al.[37] and Harrington et al.[38] this conclusion is supported by incremental cost and sensitivity analyses, while in Deitelzweig et al.[39] medical costs were reduced with the use of all three OAC, the largest reduction being seen with apixaban. Finally, in Kansal et al.'s model of the Canadian setting,[40] dabigatran was more cost-effective than rivaroxaban (ICER of CAD 6889/QALY vs. CAD 22 475/QALY, respectively.

Discussion

The novel OAC have pharmacological advantages over conventional anticoagulants that generally result in clinical benefit, as shown by various trials in a range of clinical settings.[7–12]

The present review comes at a time when this pharmacological innovation is beginning to be translated into wider use of these new agents in clinical practice.

Since these new drugs are more expensive than VKA, they represent a greater cost burden on health systems and their users. The AFFORD study set out to analyze published economic evaluation studies on the novel OAC and to determine whether they are cost-effective, i.e. whether the health gains exceed the costs of these new drugs. This is the first systematic analysis of cost-effectiveness studies to calculate the mean of the most important variable, ICERs, in euros per QALY (after currency conversion when necessary). These studies, from countries around the globe (North America, Europe, Africa and Asia), differ in their economic models, study perspectives, comparators, drug prices, willingness-to-pay thresholds and presentation of results. This variability in methodology was thus a challenge in comparing the different models.

Nevertheless, the results are consistent, showing that the novel OAC are cost-effective for stroke prevention in AF patients compared to the more widely used conventional anticoagulants, particularly warfarin.

The novel OAC that were shown to be of most interest in this review were dabigatran and apixaban. The former is the subject of more studies, due in part to the fact that it is the oldest of this group. It should be borne in mind that the results of the studies analyzed here are closely related to those of clinical trials. The RE-LY trial on dabigatran in AF showed that the 150 mg dose was more effective and the 110 mg dose was safer than warfarin,[7,8] and the 150 mg dose and the age-adjusted dose were also cost-effective in all the studies in which it was analyzed (>80% in sensitivity analysis). Apixaban was superior in both efficacy and safety to warfarin in the ARISTOTLE trial[11] and to aspirin in the AVERROES trial.[10]

It is difficult to compare the results of the models that analyze the three drugs separately, since these are based on studies and trials that use different methodologies, including different study perspectives – payer, health system, or societal. The perspectives of the payer and the health system can be considered equivalent, since the payer perspective can include insurers, employers and the state, which runs the health system in most countries. The societal perspective is wider, since it considers the benefits to the community as a whole; in theory, all costs – both direct and indirect – are included in an economic evaluation from a social perspective.[3]

This review includes three studies[37–39] that analyzed all three novel OAC, and established a hierarchy of pharmacoeconomic performance. Despite differences between the studies, they all point to the same conclusion: the new OAC are cost-effective, and apixaban is the most cost-effective, followed by dabigatran and rivaroxaban. Deitelzweig et al.[39] report that all three OAC have a negative incremental cost and therefore produce savings.

Another point in common between most of these studies is the model used for the economic analysis, which was a Markov model in over 90%. This statistical model simulates patients' clinical course in cycles to the end of their lives; in each cycle a specified probability is applied of the mutually exclusive occurrence of the major events in the population under study.[29] Different designs of the Markov model can be used and it can be adapted to different countries and different study perspectives.

The AFFORD study has certain limitations. Indirect comparisons between the novel OAC should be treated with caution due to the different methods used in clinical trials on efficacy and safety. Furthermore, there are no internationally standardized guidelines for conducting economic evaluations, which poses problems for accurate comparisons between different economic models.[41] This lack of standardization needs to be remedied, as the increasing concern with containing costs and rationalizing health resource use is leading to a proliferation of economic analyses that must follow generally agreed rules if they are to be comparable.

Another important limitation of the AFFORD study is that some of the authors of the studies included in the review are employed by the laboratories that produce the drugs under study, which could give rise to conflicts of interest.

Conclusion

The AFFORD study demonstrates that novel OAC are cost-effective compared to conventional antithrombotic therapies despite their high cost, in a variety of geographic and social contexts, and when analyzed by different pharmacoeconomic methodologies.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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