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Cost-effectiveness of New Oral Anticoagulants for the Prevention of Stroke in Patients with Atrial Fibrillation in Low and Middle-Income Countries: A Systematic Review

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Abstract

Background: Low- and middle-income (LMICs) countries are facing with a high incidence of cardiovascular diseases and limited resources for confronting these diseases. Atrial fibrillation(AF) is the most common cardiac arrhythmia in the world that is associated with significant morbidity and mortality. This study assessed cost-effectiveness studies of novel oral anticoagulants(NOACs) compared to Warfarin for the prevention of stroke in patients with AF in LMICs.

Methods: In this systematic review study, electronic databases were searched for economic evaluation studies about NOACs cost-effectiveness conducted in LMICs between 2008 and 2019. The selection of studies for review was also based on the PICO (population, intervention, comparison, and outcomes) guidelines. In this study, the population was restricted to patients with atrial fibrillation living in LMICs. We identified three types of drugs (apixaban, rivaroxaban, dabigatran, and edoxaban) as interventions and warfarin as the comparison therapy. Quality of Health Economic Studies checklist was used to evaluate the quality of the included articles.

Results: Sixteen articles were extracted, including four cost-effectiveness analyses and two cost-utility analyses. QHES scores ranged from 58 to 87.5 out of a possible 100 points, with a mean score of 77.34. The results of the study showed that from a social perspective, Edoxaban is the most cost-effective therapeutic option compared to warfarin and other NOACs, but Warfarin was much more cost-effective than Rivaroxaban and Apixaban. Furthermore, NOACs were more cost-effective than warfarin from the payer perspective, but from the health system perspective, all NOACs were dominated by warfarin.

Conclusion: The present systematic review demonstrates that from a social perspective, Edoxaban is the optimal alternative to warfarin other NOACs for stroke prevention in patients with AF in (LMICs). one study was found on the economic evaluation of NOACs and warfarin in patients with AF in low-income countries, so further research on the economic evaluation of these drugs is recommended.

Keywords: Economic Evaluation, New Oral anticoagulant, Warfarin, Atrial fibrillation

Conflicts of Interest: None declared
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Introduction

Atrial fibrillation(AF) is well known as the most common arrhythmia in adults, which increases the risk of stroke, heart failure, valvular heart d isease, and other thromboembolic complications (1, 2). Thus AF is respon-

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↑What is "already known" in this topic:
In recent years, NOACs have been developed as alternatives to warfarin, including Apixaban, Dabigatran, Edoxaban, and Rivaroxaban. Their use is expected to help overcome warfarin's limitations. There is still uncertainty about the use of NOACs. Certain populations, such as those with severe renal impairment, have limited safety data on NOACs.

→What this article adds:
From a social perspective, the present systematic review demonstrates that Edoxaban is an optimal alternative to warfarin and other NOACs for stroke prevention in patients with AF living in LMICs.

sible for substantial morbidity, disability, and mortality (3, 4). Due to the abnormal cardiac rhythm in patients with AF, blood flow through heart chambers becomes turbulent and it increases the risk of thrombus formation in the heart subsequently. This thrombus then can be dislodged and block the blood flow to the vital organs, thus eventually leading to stroke (5, 6).

The incidence and prevalence of arrhythmias increase exponentially with age (7). According to present evidence, 10 percent of the population over 80 years of age have AF (8). The burden of AF varies in different regions, and its incidence and prevalence are higher in high-income countries compared to developing countries. The lower rates of AF in developing countries may be due to limited access to health services and underreporting (9). The prevalence of AF in Thailand is reported to be between 0.4 and 2.2 percent, which increases up to 2.8 percent in the late elderly. Also, the prevalence of this disease in Malaysia is estimated at 0.5-0.7 percent (10).

Higher rates of AF and heart failure have been reported in the younger population and in low-income countries compared to high-income countries, with a stroke prevalence ranging from 10 to 27 percent (9-11). In addition, the high burden of AF increases the utilization of health care resources. Stroke is costly from the individual, family, and social aspects (12). Statistics show that about one-third of hospitalizations are due to episodes of cardiac arrhythmias caused by the disease with an increased rate of 66% over the last 20 years. 27% of GDP and about 3% of health expenditures are spent on the treatment and care of stroke (13). The total cost of AF care in Korea is estimated at about € 388.4 million in 2015, which is equivalent to 0.78% of Korea's total national health insurance expenditure (14).

Prevention of stroke is the main priority in the management of AF (15). Traditionally, vitamin K antagonists have been used to reduce the risk of stroke and mortality in these patients (16). These anticoagulants are used to prevent blood clots formation and reduce the risk of stroke (17). These include warfarin and new oral anticoagulants(NOACs) (18). Warfarin has a narrow therapeutic window, and changes in dose-response require frequent monitoring and dose adjustment (17, 19).

Warfarin use is challenging because over-dose of the drug could be life-threatening in some cases, and under-dose treatment does not meet the therapeutic goals (20). The most important side effect of warfarin is bleeding, which is directly related to its dose (21). In recent years, with the advent of NOACs, including Apixaban, Dabigatran, Edoxaban, and Rivaroxaban, they have been introduced as alternatives for warfarin and are expected to overcome warfarin limitations (22). Uncertainty still remains about the use of NOACs. Safety data of NOACs are still limited in certain populations, such as those with severe renal insufficiency. NOACs have high purchase costs that can limit their access, especially in low-income countries (23).

Policymakers can use economic evaluation analysis to decide how to allocate resources. The purpose is to determine whether the health gains offered by an intervention are sufficient to justify adoption relative to any additional costs (24). In determining whether health interventions are cost-effective, cost-effectiveness thresholds are important decision criteria (25). The World Health Organization (WHO) recommends thresholds around one to three times the gross domestic product (GDP) per capita for low- and middle-income countries (24).

To our knowledge, this is the first systematic review to identify and examine comparative studies about the economic evaluation of NOAC in the prevention of stroke in patients with AF in low and middle countries. We evaluated and compared the cost-effectiveness evidence of NOAC for the prevention of stroke in patients with AF, considering the uncertainties in the literature.

Methods

Searching strategy and inclusion criteria

This systematic review study was conducted in 2021. Adhering to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, we performed a systematic review with a priori design to identify systematic reviews of economic evaluation of anticoagulants in AF patients (26). The protocol was registered in the PROSPERO (International prospective register of systematic reviews) under the following registration number: CRD42020179538.

A literature search was performed between January 2008 and July 2020 using Cochrane Library, Medline/PubMed, Web of Science, Scopus, and Embase for possible studies. The reference lists of the retrieved articles were also studied. The start date of the databases search strategy was established based on the first published study of outcomes of Dabigatran (the first NOAC). There were no limitations regarding language and publication status in this study. The search strategy included specific keywords and combined Medical Subject Headings (Mesh) headings using the following terms: The keywords used to identify articles were: cost, cost-effectiveness and anticoagulant agents. A search strategy including keywords was presented in the supplementary material section (Appendix S1). We defined review inclusion and exclusion criteria to be as relevant as possible in terms of the PICOS (population, intervention, comparison, outcomes, and study design) framework. The inclusion criteria of studies were as follows: (1) population: patients with atrial fibrillation in LMICs. LMICs were defined according to the World Bank (Appendix S2), (2) interventions: rivaroxaban, dabigatran, apixaban, or edoxaban, (3) comparator: warfarin, and (4) outcomes: Incremental cost-effectiveness ratio (ICER), Incremental cost per quality-adjusted life years (QALY), Net monetary benefit 5) Full economic evaluation studies: cost-effectiveness analysis (CEA), cost-utility analysis (CUA) or cost-benefit analysis (CBA). The exclusion criteria were as follows: 1) Letters to editors, review articles, conference abstracts. Search results were imported into EndNote X7, where duplicates were identified and removed. Titles and abstracts and, then the full text of the included studies were screened according to inclusion and exclusion criteria.

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Screening and data extraction

One reviewer screened relevant studies based on title and abstract. The full text of the studies was evaluated by two independent authors (AS and AA) to confirm their eligibility. Areas of disagreement were resolved by discussion until consensus was reached. In cases where the disagreement could not be resolved, the viewpoints of a third reviewer were used.

The following information was extracted: author, journal, country of origin, year of publication, type of economic evaluation, compared interventions, measured outcomes, time horizon, funding source, discount rate, Analysis of uncertainty, summarized result, and main finding of the study.

Quality assessment

We used the Quality of Health Evaluation Studies (QHES) scale to assess included studies (27). The QHES scale is a 16-item scale that each item has 1 to 9 points for each criterion, which are used to generate a total score 100-point scale. Using the QHES score for economic studies, the quality of the studies was shown as follows: poor (QHES<25), low (QHES score≥ 25 and <50), average (QHES score ≥ 50 and <75), and high quality (QHES score ≥75 and ≤100). Two reviewers (A.S and A.A) assessed the quality of studies independently. A third reviewer would contribute whenever a disagreement occurred.

Data analysis

Outcomes of the studies were measured by using the ICER, which includes cost per life-year gained, cost per case averted, cost per QALY, and cost per DALY. Cost results of studies were adapted to 2019 international dollars to facilitate comparisons between studies on the data of the international monetary fund. Finally, results were presented using a narrative approach.

Results

Overview

We selected a total of 3415 articles after the removal of duplicates (Fig. 1). After reviewing the titles and abstracts, 670 papers were included for full-text. At the end of this process, 16 publications were included in the qualitative analysis. The characteristics of the articles included in this review are presented in Tables 1 and 2. The PRISMA flow diagram of this study is illustrated in Figure 1.

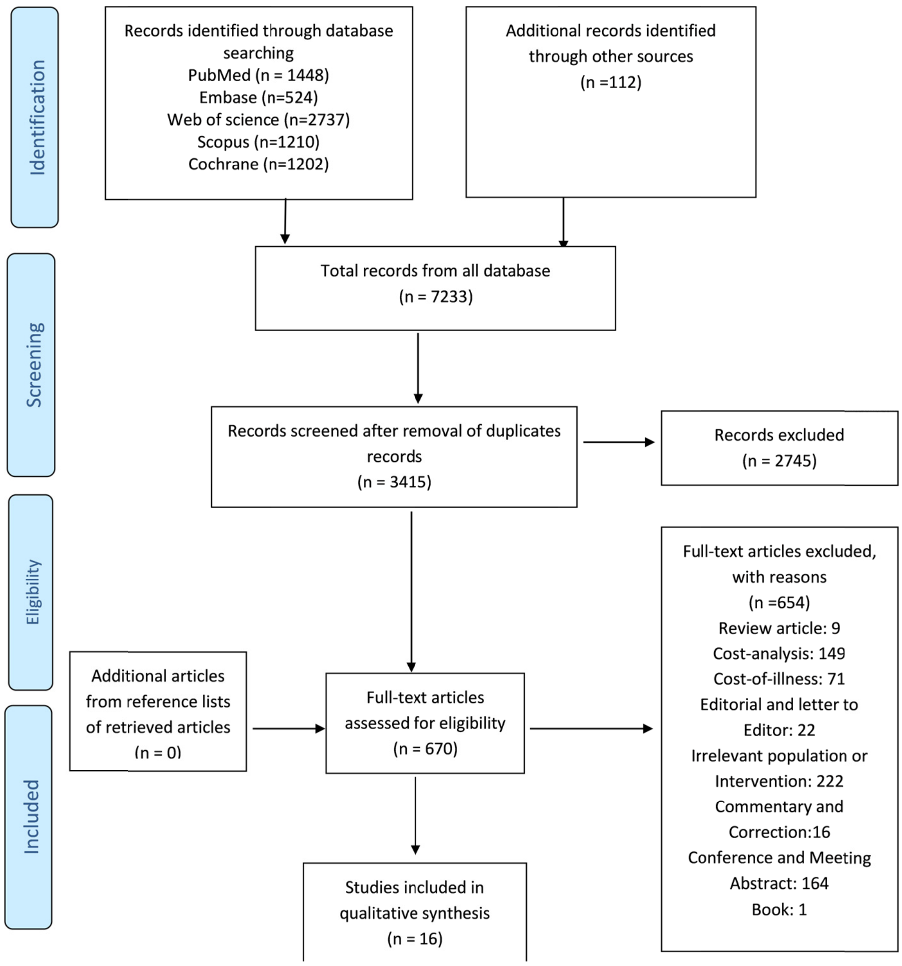

Fig. 1. PRISMA flow chart for study selection

Table 1 .Study design and setting overview

Reference (year of publication)	Costing year	Setting	Compared intervention	Type of economic evaluation(model)	Perspective	Time horizon	Discount rate(%)	Sensitivity analyses	Industry sponsorship	QHES score
Belousov, Yu B. (2012)	2011	Russia	Dab 150 mg ,War	CEA (Markov)	Payer	lifetime	3.5	Yes, one-way, PSA	Yes	77.5
Bergh, M. (2013)	2011	South Africa	Dab 110, 150 mg ,War	CUA (Markov)	Payer	Lifetime	NR	Yes, one-way	Yes	69.25
Jarungsuccess, S. (2014)	2013	Thailand	Dab 150,Dab 110,Riv 20 mg, Apix 5 mg, War	CUA (Markov)	Health care system and societal	Lifetime	3	Yes, PSA	No	83
Wu, B. (2014)	2012	China	ASP, ASP plus clop, War,Riv No intervention	CUA (Markov)	Health care system	Lifetime	3	Yes , on-way and PSA	No	78.5
A.V. Rudakova (2014)	2013	Russia	Apix 5mg,War 5 mg,ASA 100 mg	CUA (Markov)	Health care system	Lifetime	3.5	Yes , one-way	Yes	59
Giorgi, M. A. (2015)	2012	Argentina	Apix,War	CEA CUA (Markov)	Payer	Lifetime	5	Yes , on-way and PSA	No	85.5
Triana, Juan J. (2016)	2014	Colombia	Dab 110 mg, Dab 150 mg, War	CUA (Markov)	Payer	Lifetime	5	Yes, one-way	Yes	58
García-Peña. (2017)	2014	Colombia	Dab 150 mg, Apix 5 mg ,Riv 20 mg,War (5-10) mg	CUA (Markov)	Payer	Lifetime	3	Yes , on-way and PSA	No	76.5
Nedogoda, S. V. (2017)	2015	Russia	Riv 20 mg,Apix 5 mg	CEA (Decision tree)	NR	One year	Not applicable	Yes , on-way	No	63
Dilokthornsakul, P. (2019)	2017	Thailand	Dab 110 mg ,Dab 150 mg ,Riv 20 mg ,Apix 5 mg ,Edo 60 mg ,Edo 30 mg ,War	CUA (Markov)	Social	Lifetime	3	Yes , on-way and PSA	Yes	82.5
Dwiprahasto, Iwan (2019)	2012	Indonesia	Riv 15 mg ,Riv 20 mg ,War	CUA (Markov)	Payer	Lifetime	3	Yes , on-way and PSA	Yes	87.5
Kim, H. (2019)	2017	Korea Republic	Riv 15 mg ,Riv 20 mg ,War	CUA (Markov)	Social	Lifetime	5	Yes, PSA	No	79

Dab: Dabigatran, Riv: Rivaroxaban, Apix: Apixaban, Edox: Edoxaban, War: Warfarin, Clop: Clopidogrel, PSM : Patient self-management ,PST: Patient self testing, LAAC : Left atrial appendage closure , PSA: Probabilistic sensitivity Analysis, NR: Not reported

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Reference (year of publication)	Costing year	Setting	Compared intervention	Type of economic evaluation(model)	Perspective	Time horizon	Discount rate(%)	Sensitivity analyses	Industry sponsorship	QHES score
Mendoza, José A. (2019)	2015	Colombia	Dab 150 mg ,Apix 5 mg ,Riv 20 mg ,War	CUA (Markov)	Payer	10 years	3	Yes , on-way and PSA	No	71
Rattanachotphanit, T. (2019)	2017	Thailand	Apix 5 mg ,Riv 20 mg ,Edox 39 mg,Edox 60 mg ,Dab 110 mg ,Dab 150 mg ,War	CUA (Markov)	Payer and social	20 years	3	Yes , on-way and PSA	No	82.5
Dong, S. J. (2020)	2016	China	Dab 150 mg, 110 mg ,Riv 20 mg	CUA (Markov)	Health care system	Lifetime	5	Yes , on-way and PSA	Yes	85.5
Ng, S. S. (2020)	2019	Thailand	Usual War, Genotype-guide ,PSM, PST ,Riv 20 mg ,Apix 5 ,mg ,Edox 60 mg ,Dab 150 mg ,LAAC	CUA (Markov)	Health care and social	Lifetime	3	Yes , on-way and PSA	No	84.5

Dab: Dabigatran, Riv: Rivaroxaban, Apix: Apixaban, Edox: Edoxaban, War: Warfarin, Clop: Clopidogrel, PSM : Patient self-management ,PST: Patient self testing, LAAC : Left atrial appendage closure , PSA: Probabilistic sensitivity Analysis, NR: Not reported

Table 2. Intervention cost and output results

Reference	Intervention	Cost(US$ 2019)	Mean QALY/YLG/Fatal death			Cost-effectiveness measure (US$ 2019)
			QALY	YLG	Fatal death	
Belousov, Yu B. (2012)	Dab 150 mg	107126.75	_	_	1.15	ICER(cost per one additional life year : 30470.67
	War	110494.88	_	_	1.26	
Bergh, M. (2013)	Dab 110, 150 mg	76815.56	7.19	9.33	_	Cost per QALY : 22374.14
	War	72260.62	6.98	9.14	_	

ICER: Incremental cost-effectiveness, Riv: Rivaroxban, Dabi: Dabigatran, Apix: Apixaban, War:Warfarin, Edox: Edoxaban.YLG : Years life gained ,QALY: Quality adjusted-life years, PSM : Patient self-management ,PST: Patient self testing, LAAC : Left atrial appendage closure , Clop: Clopidogrel,Asp: Aspirin

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Reference	Intervention		Cost (US$ 2019)	Mean QALY/YLG/Fatal death			Cost-effectiveness measure (US$ 2019)
				QALY	YLG	Fatal death	
		Dab 150 mg	16655.37	2.34	_	_	ICER Dab 150 vs. war: 202455.82
		Dab 110 mg	16745.66	2.29	_	_	ICER Dab 110 vs. war: 4142998.59
	Health care system perspective	Riv 20 mg	15451.38	2.31	_	_	ICER Riv 20 mg vs. war: 450668.43
		Apix 5 mg	26729.78	2.33	_	_	ICER Apix 5 mg vs. war: 498287.99
		War	6352.30	2.29	_	_	
		Apix 5 mg	29966.23	2.34	_	_	ICER Dab 150 vs. war: 201045.84
		Dab 150	30096.81	2.29	_	_	ICER Dab 110 vs. war: 4130454.59
Jarungsuccess, S. (2014)	Social Perspective	Dab 110	28798.05	2.31	_	_	ICER Riv 20 mg vs. war:448888.02
		Riv 20 mg	40044.99	2.33	_	_	ICER Apix 5 mg vs. war: 496639.55
		War	19734.91	2.29	_	_	
		No intervention	3948.93	10.44	_	_	ICER No vs. Riv: -1195631.66
		Asp	6530.61	10.08	_	_	ICER Asp vs. Riv: 449928.24
		Asp plus clop	18679.60	9.91	_	_	ICER Asp plus clop vs. Riv: 244336.89
	$CHADS_2$ Score 0	War	8461.83	9.8	_	_	ICER War vs. Riv: 213055.55
		Riv	123512.09	10.34	_	_	
		No intervention	4310.68	9.82	_	_	ICER No vs. Riv: 553132.85
		Asp	6556.45	9.68	_	_	ICER Asp vs. Riv: 325463.47
	$CHADS_2$ Score 1	Asp plus clop	18439.18	9.68	_	_	ICER Asp plus clop vs. Riv: 291512.81
		War	8343.86	9.5	_	_	ICER War vs. Riv: 211555.75
		Riv	120468.67	10.03	_	_	
	$CHADS_2$ Score 2	No intervention	4721.86	9.15	_	_	ICER No vs. Riv: 188798.02
		Asp	6847.43	9.19	_	_	ICER Asp vs. Riv: 198487.78
		Asp plus clop	18302.12	9.25	_	_	ICER Asp plus clop vs. Riv: 199396.65
		War	8357.34	9.22	_	_	ICER War vs. Riv: 206874.33
		Riv	118000.45	9.75	_	_	
	$CHADS_2$ Score 3	No intervention	5375.71	8.83	_	_	ICER No vs. Riv: 131313.33
		Asp	7618.11	9.05	_	_	ICER Asp vs. Riv: 172948
		Asp plus clop	18421.21	9.12	_	_	ICER Asp plus clop vs. Riv: 175234.61
		War	8967.38	9.24	_	_	ICER War vs. Riv: 242971.90
Wu, B.		Riv	118304.90	9.69	_	_	
(2014)	$CHADS_2$ Score 4	No intervention	5794.76	7.86	_	_	ICER No vs. Riv: 83752.07
		Asp	7491.16	8.2	_	_	ICER Asp vs. Riv: 112547.22
		Asp plus clop	17724.67	8.46	_	_	ICER Asp plus clop vs. Riv: 140948.04
		War	8692.13	8.63	_	_	ICER War vs. Riv: 206935
		Riv	112159.63	9.13	_	_	
	$CHADS_2$ Score 5	No intervention	5726.22	6.09	_	_	ICER No vs. Riv: 56697.15
		Asp	6884.50	6.56	_	_	ICER Asp vs. Riv: 79869.43
		Asp plus clop	14998.06	6.97	_	_	ICER Asp plus clop vs. Riv: 115569.43
		War	7586.66	7.35	_	_	ICER War vs. Riv: 281141.12
		Riv	94740.54	7.66	_	_	
	$CHADS_2$ Score 6	No intervention	3308.56	3.33	_	_	ICER No intervention vs. Riv: 59804.61
		Asp	3327.66	3.6	_	_	ICER Asp vs. Riv: 93405.88
		Asp plus Clop	7465.33	3.81	_	_	ICER Asp plus clop vs. Riv: 150729.92
		War	2990.62	3.93	_	_	ICER War vs. Riv: 301144.14
		Riv	48162.30	4.08	_	_	

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			QALY	YLG	Fatal death	
A.V. Rudakova (2014)	Apix	10173.14	4.768	6.653	_	Cost per QALY: Apix vs. War :34688.97
	War	3698.54	4.582	6.466	_	Cost per QALY :Apix vs. ASA : 27170.12
	ASA	3224.09	4.380	6.167	_	
Giorgi, M. A. (2015)	War	Net Cost Apix-War:151.73		_	_	Cost per Life Year gained Apix-War: 924.93
	Apix 5 mg	Net Life Years Apix-War: 0.164		_	_	Cost per QALY gained Apix-War:883.12
		Net QALYs Apix-War: 0.172				Cost per Stroke Avoided Apix-War:6091.36
Triana, Juan J. (2016)	War	9781505090.01	7.31	_	_	ICER per QALY Dab 150 mg vs. War: 250097279.67 ICER per QALY Dab 110 mg vs. War : 37043868.58
	Dab 150 mg	111652963.25	7.86	_	_	
	Dab 110 mg	113560248.26	7.73	_	_	
García-Peña. (2017)	War (5-10) mg	3841694.05	3.5144	_	_	ICER per QALY Dab 150 mg vs. War: 91709481.67
	Dab 150 mg	10731460.31	3.5895	_	_	ICER per QALY Riv 20 mg vs. War: 83926868.48
	Riv 20 mg	10799546.71	3.5973	_	_	ICER per QALY Apix 5 mg vs. War : 141868136.92
	Apix 5 mg	13021508.24	3.5791	_	_	
Nedogoda, S. V. (2017)	Riv 20 mg	2451.21	_	_	_	Apix vs. War ,and ASA was dominant .
	Apix 5 mg	2474.41	_	_	_	
Dilokthornsakul, P. (2019)	War	13264.09	6.98	9.28	_	Cost per QALY Dab 150 mg vs. war: 36228.94 Cost per QALY Dab 110 mg vs. war: 39293.60
	Dab 150 mg	40227.91	7.28	9.58	_	Cost per QALY Apix 5 mg vs. war: 22752.50 Cost per QALY Riv 20 mg vs. war: 44299.82
	Dab 110 mg	40423.18	7.26	9.57	_	Cost per QALY Edox 60 mg vs. war: 29972.06
	Apix 5 mg	38266.45	7.42	9.75	_	Cost per QALY Edox 30 mg vs. war: 30036.58
	Riv 20 mg	38043.29	7.20	9.49	_	
	Edo 60 mg	38265.95	7.31	9.63	_	
	Edo 30 mg	37638.05	7.30	9.63	_	
Dwiprahasto, Iwan (2019)	Riv 15 ,20 mg	14623.06	4.79	_	_	Cost per QALY Riv vs. War : 43399.84
	War	6636.83	4.61	_	_	
Kim, H. (2019)	Riv 15 ,20 mg	21736.74	11.81	_	_	Cost per QALY Riv vs. War : 10102.39
	War	17849.60	11.43	_	_	

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				QALY	YLG	Fatal death	
Mendoza, José A. (2019)	Apix 5 mg		19207.87	1.48	_	_	Cost per QALY Dab 150 mg vs. Apix 5 mg: 13935.24 Cost per QALY Riv 20 mg vs. Apix 5 mg: -23108.19
	Dab 150 mg		19428.72	1.49	_	_	Cost per QALY war vs. Apix 5 mg: -27377.32
	Riv 20 mg		26317.01	1.24	_	_	
	War		22645.04	1.32	_	_	
	Societal perspective	War	4789.45	6.10	7.95	_	Cost per QALY Riv 20 mg vs. war: 18069.20
		Apix 5 mg	12125.58	6.44	8.10	_	Cost per QALY Apix 5 mg vs. war: 21608.73
		Riv 20 mg	12162	6.51	8.08	_	Cost per QALY Edox 30 mg vs. war: 20865.65
		Edox 30 mg	12252.54	6.45	8.12	_	Cost per QALY Edox 60 mg vs. war :10099.27
		Edox 60 mg	12313.9	6.84	8.54	_	Cost per QALY Dab 110 mg vs. war: 16480
		Dab 110 mg	12565.81	6.57	8.26	_	Cost per QALY Dab 150 mg vs. war: 11609.37
		Dab 150 mg	12663.63	6.78	8.48	_	
	Payer perspective	War	3748.72	6.10	7.59		Cost per QALY Riv 20 mg vs. war: 18077.52
		Apix 5 mg	11119.19	6.44	8.10	_	Cost per QALY Apix 5 mg vs. war: 21706.56
		Riv 20 mg	11125.43	6.51	8.08	_	Cost per QALY Edox 30 mg vs. war: 20630.44
Rattanachotphanit, T. (2019)		Edox 30 mg	11128.55	6.45	8.12	_	Cost per QALY Edox 60 mg vs. war:1021.19
		Edox 60 mg	11362.72	6.84	8.54	_	Cost per QALY Dab 110 mg vs. war: 16598.64
		Dab 110 mg	11581.27	6.57	8.26	_	Cost per QALY Dab 150 mg vs. war: 11775.89
		Dab 150 mg	11737.38	6.78	8.48	_	
Dong, S. J. (2020)	Dab 150, 110 mg		74412.20	7.95	10.38		Cost per QALY Riv vs Dab : 34232.62
	Riv 20 mg		65884.22	7.70	10.14		
	Societal perspective	Usual War	1421	15.87	21.24	_	Cost per QALY GP vs. usual war: 3025
		Genotype-guide	1498	15.89	21.27	_	Cost per QALY PSM vs. usual war:1395
		PSM	2109	16.36	21.96	_	Cost per QALY PST vs. usual war: -4575
		PST	2427	15.65	20.91	_	Cost per QALY Riv vs. usual war: 14247
		Riv 20 mg	5806	16.18	21.69	_	Cost per QALY Apix vs. usual war: 8678
		Api 5 mg	6006	16.40	22.02	_	Cost per QALY Edox vs. usual war: 10186
		Edox 60 mg	6039	16.32	21.91	_	Cost per QALY Dab vs. usual war: 12454
		Dab 150 mg	6375	16.27	21.83	_	Cost per QALY LAAC vs. usual war : 13982
		LAAC	9409	16.44	22.09	_	
	Health care perspective	Usual War	868	15.87	21.24	_	Cost per QALY GP vs. usual war: 3533
		Genotype-guide	958	15.89	21.27	_	Cost per QALY PSM vs. usual war: 1951
		PSM	1831	16.36	21.96	_	Cost per QALY PST vs. usual war: -5815
		PST	2148	15.65	20.91	_	Cost per QALY Riv vs. usual war: 15126
		Riv	5525	16.18	21.69	_	Cost per QALY Apix vs. usual war: 9188
		Api	5724	16.40	22.02	_	Cost per QALY Edox vs. usual war: 10780
		Edox	5757	16.32	21.91	_	Cost per QALY Dab vs. usual war: 13131
		Dab	6092	16.27	21.83	_	Cost per QALY LAAC vs. usual war : 14564
Ng, S. S. (2020)		LAAC	9185	16.44	22.09	_	

Sixteen articles were included in this review, which were published between 2012 and 2020. Most of these studies were from Thailand (n=4) (28-31), Russia (n=3) (32-34), Colombia (n=3) (34-36), China (n=2) (37, 38), Indonesia (n=1) (37-39), Argentina (n=1) (40), Korea (n=1) (41) and South Africa (n=1) (42). Most of the studies (n=8) were conducted from the payer prospective (30, 32, 34-36, 39, 40, 42). Five studies were designed in a health system perspective (28, 31, 33, 37, 38), while five studies had a societal perspective (28-31, 41). The perspective of one study was not mentioned at all (43).

Studies from Thailand used the following Willingness-to-pay thresholds THB 160000/QALY (29, 31), and $50000/QALY (30). The thresholds adopted by studies from Russia was 104 million rubles/QALY (33), Colombia was $ 22500/QALY (36), $ 9000/QALY (34); China $16350 /QALY (38), ¥61940/ QALY (37), Indonesia IDR 133375000/QALY (39), Argentina $11558/QALY (40), Korean $30000/QALY (41). Three studies have not stated the Willingness-to-pay threshold (32, 42, 43).

Decision-analytic modeling was used for economic evaluation analysis in all studies. Fifteen studies applied the Markov model to outcomes over a time horizon of 10, 20 years, and lifetime (28-42). One study developed decision trees to depict the time horizon of one year (43). Discounting rate for costs and benefits varied between 3 - 5 % annually.

Assessment of Methodological Quality

The total score for each study is presented in Table 3. The mean QHES scale scores for all the 16 studies was 77.34 ± 8.36 out of 100, ranging from 58 to 87.5. Twelve studies scored in the range of 75 to 100 and were rated as high quality (28-33, 35, 37-41), and the remaining four studies evaluations score was within 50 to 74 (average quality) (34, 36, 42, 43).

Figure 2 displays each QHES question and how many studies its criterion had. In questions 4,12,15 and 16, the studies had a total score of 100% for economic evaluations. None of these studies obtained all the scores for question 5, and only one study scored total points for question 14 (37). Nevertheless, most of the studies were well designed and eventually, in 10 out of 16 items, more than 75% of the articles received the full score.

Cost-Effectiveness Results

Most of the studies that compared economic evaluation of Dabigatran versus Warfarin were done using a payer perspective, and in 100% (n=6/6) of the studies, the final conclusion was that dabigatran is a cost-effective strategy (30, 32, 34-36, 42). Besides, in four studies that analyzed the cost-effectiveness of Dabigatran versus warfarin from a social perspective, warfarin was dominant in 50% (n=2/4) of studies (28, 31). In Studies with health care system perspective warfarin was an optimal choice in terms of economic evaluation (28, 31).

Also, in articles that evaluated the cost-effectiveness of Rivaroxaban versus warfarin from the payer and social perspectives, Rivaroxaban was dominant in 66% (n=2/3) (35, 39) and 40% (n=2/5) of the studies, respectively (29, 41). Besides, analysis of the studies with a health system perspective showed that warfarin was dominant in 100% (n=3/3) of studies compared to Rivaroxaban (28, 31, 38). Among studies that analyzed the cost-effectiveness of Apixaban vs. warfarin from the healthcare system and payer perspectives, Apixaban was dominant in %33 (n=1/3) (33), and %50 (n=2/4) of studies, respectively (34, 40). In studies with a social perspective, warfarin was dominant in 73% (n=3/4) of studies versus Apixaban (28, 30, 31). also, in studies that compared the cost-effectiveness of Edoxaban vs. warfarin from a social perspective, Edoxaban was dominant in %66 (n= 2/3) of studies (29, 30). Moreover, from a healthcare and payer perspective Edoxaban was dominated by warfarin (30, 31).

Drivers of Cost-Effectiveness

In 14 of the 16 studies included, one-way sensitivity analyses were reported. In addition, numerous studies haven't assessed one-way sensitivity on all model parameters or have only examined a small number of input parameters in a one-way sensitivity analysis. Among the 16 included studies, the model was most sensitive to the probability of intracranial hemorrhage and gastrointestinal

Table 3. Results of the QHES instrument

Reference	Q_1	Q_2	Q_3	Q_4	Q_5	Q_6	Q_7	Q_8	Q_9	Q_{10}	Q_{11}	Q_{12}	Q_{13}	Q_{14}	Q_{15}	Q_{16}	Total
Belousov, Yu B.(2012)	7	2	8	1	4.5	6	5	7	5	4	7	5	5	0	8	3	77.5
Bergh, M.(2013)	6	2	5	1	2.25	6	2.5	3	5	6	7	8	4.5	0	8	3	69.25
Jarungsuccess, S.(2014)	7	2	6	1	3	4	5	7	7	5	7	7	7	4	8	3	83
Wu, B.(2014)	6	2	4	1	4.5	5	4	7	5	5	7	7	5	5	8	3	78.5
A.V. Rudakova (2014)	7	2	8	1	2.25	6	2.5	7	5	3	7	8	5	3	8	3	77.75
Giorgi, M. A.(2015)	7	4	3	1	4.5	6	5	7	7	6	7	6	7	4	8	3	85.5
Triana, Juan J.(2016)	7	2	2	1	2	4	3	7	3	4	7	3	2	0	8	3	58
García-Peña.(2017)	7	2	8	1	4.5	6	2	7	2	6	7	6	3	4	8	3	76.5
Nedogoda, S. V.(2017)	7	2	8	1	2	3	1	3	4	3	7	3	4	0	8	3	59
Dilokthornsakul, P.(2019)	7	2	7	1	4.5	6	4	6	5	5	7	8	5	4	8	3	82.5
Dwiprahasto, Iwan.(2019)	7	2	8	1	4.5	6	5	7	6	6	7	8	5	4	8	3	87.5
Kim, H.(2019)	7	2	5	1	3	6	3	7	6	6	7	6	5	4	8	3	79
Mendoza, José A.(2019)	7	2	8	1	4.5	2	3	4.5	3	4	7	6	5	3	8	3	71
Rattanachotphanit, T.(2019)	7	2	8	1	4.5	6	3	7	6	6	7	6	5	3	8	3	82.5
Dong, S. J.(2020)	7	2	8	1	4.5	6	3	7	5	6	7	8	4	6	8	3	85.5
Ng, S. S.(2020)	7	2	8	1	4.5	6	3	7	4	5	7	8	7	4	8	3	84.5

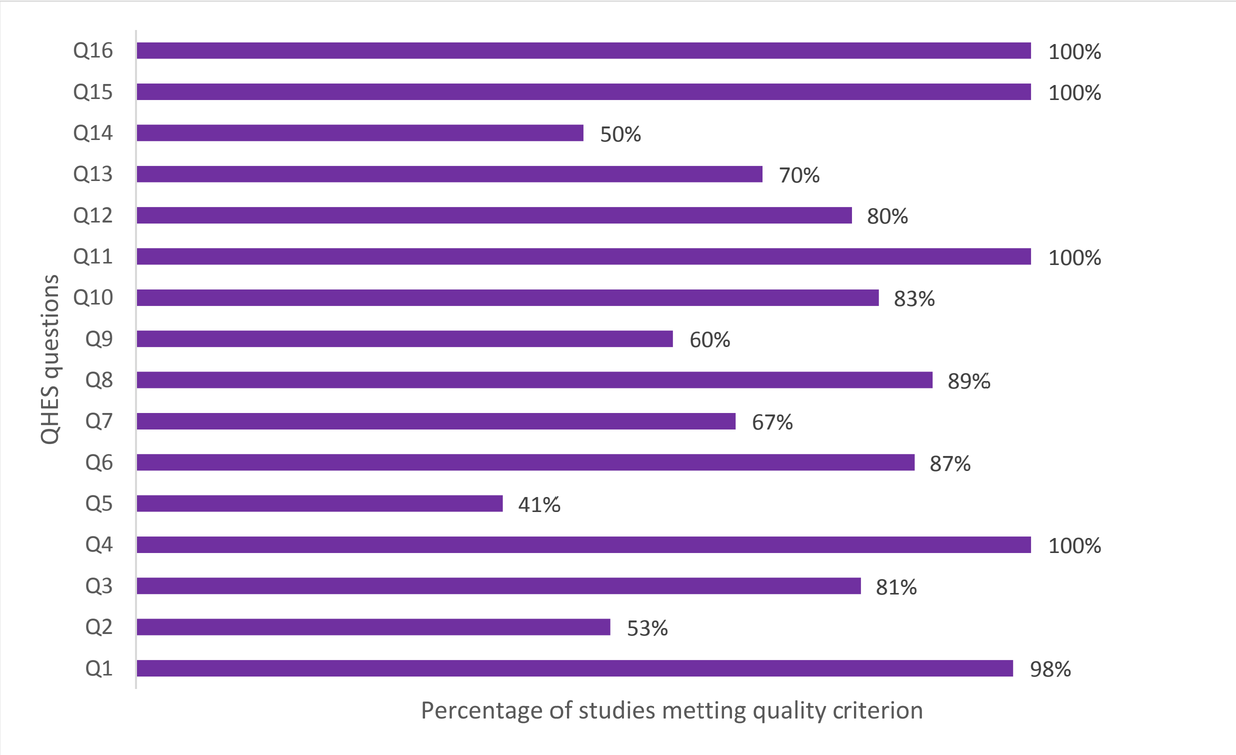

Fig. 2. Methodological quality of included studies by QHES checklist

hemorrhage, stroke probability (34, 40), cost of the medications and time distribution of the INR, hazard ratios of Myocardial infarction (29, 35, 38), and the utility decrement applied to stable warfarin patients, discontinuation rates for rivaroxaban, and for warfarin (39). Based on the other studies, model outputs were robust to both one-way and probabilistic sensitivity analyses.

Discussion

The evidence on the cost-effectiveness of NOACs for stroke prevention is growing rapidly. We conducted a systematic review of economic evaluation studies concerning interventions for the prevention of stroke in patients with AF in low and middle-income countries and identified 16 studies. Most studies were conducted in Thailand, Colombia and Russia, and had an appropriate lifetime horizon. The result of cost-effectiveness analyses suggests that edoxaban is a cost-effective therapeutic option when compared to warfarin when preventing AF-related strokes in low and middle-income countries.

Evidence has revealed that from a social perspective, only edoxaban was cost-effective compared to warfarin, but Rivaroxaban and Apixaban were dominated by warfarin. From a social perspective, edoxaban and dabigatran were better alternatives for warfarin, respectively, but in this studies the superiority of dabigatran over warfarin was unclear. In Dilokthornsakul’s study, which was conducted from a social perspective in Thailand, Apixaban was a much better alternative for warfarin than dabigatran 110, 150 mg (29). But in Rattanachotphanit's study, dabigatran was more cost-effective than Rivaroxaban and Apixaban as an alternative for warfarin (30).

NOACs were more cost-effective than warfarin from the payer perspective. Also, from this perspective, among the new anticoagulants, Edoxaban, dabigatran, Rivaroxaban, and Apixaban were better alternatives for warfarin, respectively.

All NOACs were dominated by warfarin from the health system perspective. In addition, compared to Rivaroxaban and dabigatran, Edoxaban was a more cost-effective alternative for warfarin from a health system perspective. Also, Apixaban was a better alternative for warfarin than dabigatran. In Jarungsuccess's study, dabigatran 150 mg was a better alternative to warfarin than Apixaban and Rivaroxaban in Thailand (28). Ng and et al showed that compared to warfarin, NOACs were not as cost-effective in Thailand (31).

Most of the included studies met the majority of QHES quality criteria, yet some quality items were not met. Some studies failed to state the perspectives, discount rate, and potential biases in the studies.

Sensitivity analysis was used to test and evaluate uncertainty in the results of economic evaluation studies. In most studies, deterministic and probabilistic sensitivity analyzes have been performed, but four studies were limited to deterministic analysis. The perspective of an economic evaluation study is the benefits and costs of the interventions, and it should be explicitly stated. Considering and calculating all of the potential health effects and costs from a social perspective is considered the gold standard in economic evaluation. Most studies were conducted from a payer perspective. The payer perspective ignores costs such as patient's pocket costs as well as pro-

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duction costs for patients and the community.

Study limitations

Like all studies, this study also has its limitations. We find one study from low-income countries that do not allow us to reach a broader and generalized conclusion(41). Only studies with fulltext were included, and we did not include conference and meeting abstracts. Indirect comparisons of the cost-effectiveness of NOACs need to be done with caution because they have been performed based on clinical trials with populations that are at different risk of bleeding and ischemic stroke. Furthermore, economic models, study perspectives, discount rates, and Willingness-to-pay thresholds lead to an increase in heterogeneity, which makes it impossible to directly compare the ICERs of included studies. Despite the limitations mentioned above, this review included high-quality studies, highlighting the strength of the available evidence.

Conclusion

The result of cost-effectiveness analyses suggest that from a social perspective, edoxaban is actually a cost-effective therapeutic option when compared to Warfarin for the prevention of stroke in patients with AF in Low- and middle-income countries, but Rivaroxaban and Apixaban were dominated by warfarin. NOACs were more cost-effective than Warfarin from the payer perspective. All NOACs were dominated by warfarin from the health system perspective.

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Conflict of Interests

The authors declare that they have no competing interests.

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Appendix S1. Search strategy of databases

Search strategy in PubMed

(Cost[ti] OR "cost analysis"[tiab] OR (Analysis[tiab] AND Cost[tiab]) OR costing[tiab] OR "Cost Comparison"[tiab] OR cost-effectiveness[tiab] OR "cost effectiveness"[tiab] OR cost-utility[tiab] OR "cost utility"[tiab] OR cost-benefit[tiab] OR "cost benefit"[tiab] OR "economic evaluation"[tiab] OR "health resource allocation"[tiab] OR "Medical Economics"[ti] OR (economic[ti] AND medical[ti]) OR economic*[ti] OR "health economics"[ti] OR pharmacoeconomic*[ti] OR "decision analysis"[tiab] OR decision-analytic[tiab]) AND (anticoagulant OR "Anticoagulation Agents" OR (Agents AND Anticoagulation) OR "Anticoagulant Agents" OR "Anticoagulant Drugs" OR (Drugs AND Anticoagulant) OR "DOAC" OR "NOAC" OR "Indirect Thrombin Inhibitors" OR (Inhibitors AND Indirect Thrombin) OR (Thrombin Inhibitors AND Indirect) OR Rivaroxaban OR Xarelto OR Warfarin OR Apo-Warfarin OR Aldocumar OR Gen-Warfarin OR Warfant OR Coumadin OR Marevan OR "Warfarin Potassium" OR (Potassium AND Warfarin) OR "Warfarin Sodium" OR (Sodium AND Warfarin) OR Coumadine OR Tedicumar OR dabigatran OR Pradaxa OR "Dabigatran Etexilate" OR (Etexilate AND Dabigatran) OR "Dabigatran Etexilate Mesylate" OR ("Etexilate Mesylate" AND Dabigatran) OR (Mesylate AND "Dabigatran Etexilate") OR pradax OR pradaxa OR prazaxa OR rendix OR Apixaban OR eliques OR eliquis OR edoxaban OR endoxaban OR lixiana OR roteas OR savaysa) AND 2008/01/01:2020/07/25 [dp]

Search strategy in Web of Science Core Collection

(TI=(Cost) OR TS =("cost analysis") OR (TS=(Analysis) AND TS=(Cost)) OR TS=(costing) OR TS=("Cost Comparison") OR TS=("health care cost") OR TS=(cost-effectiveness) OR TS =("cost effectiveness") OR TS=(cost-utility) OR TS=("cost utility") OR TS=(cost-benefit) OR TS=("cost benefit") OR TS=("economic evaluation") OR TS=("health economic") OR TS=(pharmacoeconomic) OR TS=("decision analysis") OR TS=(decision-Analytic) OR TI=(economic*)) AND (TS=(anticoagulant) OR TS=("Anticoagulation Agents") OR (TS=(Agents) AND TS=(Anticoagulation)) OR TS=("DOAC") OR TS=("NOAC") OR (TS=(Inhibitors) AND TS=("Indirect Thrombin")) OR (TS=("Thrombin Inhibitor") AND TS=(Indirect)) OR TS=(Rivaroxaban) OR TS=(Xarelto) OR TS=(Warfarin) OR TS=(Apo-Warfarin) OR TS=(Aldocumar) OR TS=(Gen-Warfarin) OR TS=(Warfant) OR TS=(Coumadin) OR TS=(Marevan) OR TS=("Warfarin Potassium") OR (TS=(Potassium) AND TS=(Warfarin)) OR TS=("Warfarin Sodium") OR (TS=(Sodium) AND TS=(Warfarin)) OR TS=(Coumadine) OR TS=(Tedicumar) OR TS=(dabigatran) OR TS=(Pradaxa) OR TS=("Dabigatran Etexilate") OR (TS=(Etexilate) AND TS=(Dabigatran)) OR TS=("Dabigatran Etexilate Mesylate") OR (TS=("Etexilate Mesylate") AND TS=(Dabigatran)) OR TS=(pradax) OR TS=(pradaxa) OR TS=(prazaxa) OR TS=(rendix) OR TS=(Apixaban) OR TS=(eliques) OR TS=(eliquis) OR TS=(edoxaban) OR TS=(endoxaban) OR TS=(lixiana) OR TS=(roteas) OR TS=(savaysa)) AND PY=(2008-2020)

Search strategy in Scopus

(TITLE (cost) OR TITLE-ABS ("cost analysis") OR (TITLE-ABS (analysis) AND TITLE-ABS (cost)) OR TITLE-ABS (costing) OR TITLE-ABS ("Cost Comparison") OR TITLE-ABS ("health care cost") OR TITLE-ABS (cost-effectiveness) OR TITLE-ABS ("cost effectiveness") OR TITLE-ABS (cost-utility) OR TITLE-ABS ("cost utility") OR TITLE-ABS (cost-benefit) OR TITLE-ABS ("cost benefit") OR TITLE-ABS ("economic evaluation") OR TITLE-ABS ("health economic") OR (TITLE-ABS (economic) AND TITLE-ABS (medical)) OR TITLE-ABS (pharmacoeconomic) OR TITLE-ABS ("decision analysis") OR TITLE-ABS(decision-analytic) OR TITLE(economic*)) AND (TITLE-ABS (anticoagulant) OR TITLE-ABS ("Anticoagulation Agents") OR (TITLE-ABS (Agents) AND TITLE-ABS (Anticoagulation)) OR TITLE-ABS ("Anticoagulant Agents") OR TITLE-ABS ("Anticoagulant Drugs") OR (TITLE-ABS (Drugs) AND TITLE-ABS (Anticoagulant)) OR TITLE-ABS ("DOAC") OR TITLE-ABS ("NOAC") OR TITLE-ABS ("Indirect Thrombin Inhibitors") OR TITLE-ABS (rivaroxaban) OR TITLE-ABS (xarelto) OR TITLE-ABS(Warfarin) OR TITLE-ABS(Apo-Warfarin) OR TITLE-ABS(Aldocumar) OR TITLE-ABS(Gen-Warfarin) OR TITLE-ABS(Warfant) OR TITLE-ABS (Coumadin) OR TITLE-ABS (Marevan) OR TITLE-ABS ("Warfarin Potassium") OR (TITLE-ABS (Potassium) AND TITLE-ABS (Warfarin)) OR TITLE-ABS ("Warfarin Sodium") OR (TITLE-ABS (Sodium) AND TITLE-ABS (Warfarin)) OR TITLE-ABS (Coumadine) OR TITLE-ABS (Tedicumar) OR TITLE-ABS (dabigatran) OR TITLE-ABS (pradaxa) OR TITLE-ABS ("Dabigatran Etexilate") OR TITLE-ABS("Dabigatran Etexilate Mesylate") OR TITLE-ABS (pradax) OR TITLE-ABS (pradaxa) OR TITLE-ABS (prazaxa) OR TITLE-ABS (rendix) OR TITLE-ABS (apixaban) OR TITLE-ABS (eliques) OR TITLE-ABS (eliquis) OR TITLE-ABS (edoxaban) OR TITLE-ABS (endoxaban) OR TITLE-ABS (lixiana) OR TITLE-ABS (roteas) OR TITLE-ABS (savaysa)) AND (PUBYEAR > 2007 AND PUBYEAR < 2021)

Search strategy in Embase

(Cost:ti OR "cost analysis":ab,ti OR (Analysis:ab,ti AND Cost:ab,ti) OR costing:ab,ti OR "Cost Comparison":ab,ti OR "health care cost":ab,ti OR cost-effectiveness:ab,ti OR "cost effectiveness":ab,ti OR cost-utility:ab,ti OR "cost utility":ab,ti OR cost-benefit:ab,ti OR "cost benefit":ab,ti OR "economic evaluation":ab,ti OR "health resource allocation":ab,ti "health economic":ab,ti OR (economic:ab,ti AND medical:ab,ti) OR pharmacoeconomic:ab,ti OR "decision analysis":ab,ti OR decision-analytic:ab,ti OR economic*:ti) AND (anticoagulant:ab,ti OR "Anticoagulation Agents":ab,ti OR (Agents:ab,ti AND Anticoagulation:ab,ti) OR "Anticoagulant Agents":ab,ti OR "Anticoagulant Drugs":ab,ti OR (Drugs:ab,ti AND Anticoagulant:ab,ti) OR "DOAC":ab,ti OR "NOAC":ab,ti OR "Indirect Thrombin Inhibitors":ab,ti OR (Inhibitors:ab,ti AND Indirect Thrombin:ab,ti) OR (Thrombin Inhibitors:ab,ti AND Indirect:ab,ti) OR Rivaroxaban:ab,ti OR Xarelto:ab,ti OR Warfarin:ab,ti OR Apo-Warfarin:ab,ti OR Aldocumar:ab,ti OR Gen-Warfarin:ab,ti OR Warfant:ab,ti OR Coumadin:ab,ti OR Marevan:ab,ti OR "Warfarin Potassium":ab,ti OR (Potassium:ab,ti AND Warfarin:ab,ti) OR "Warfarin Sodium":ab,ti OR (Sodium:ab,ti AND Warfarin:ab,ti) OR Coumadine:ab,ti OR Tedicumar:ab,ti OR dabigatran:ab,ti OR Pradaxa:ab,ti OR "Dabigatran Etexilate":ab,ti OR (Etexilate:ab,ti AND Dabigatran:ab,ti) OR "Dabigatran Etexilate Mesylate":ab,ti OR ("Etexilate Mesylate":ab,ti AND Dabigatran:ab,ti) OR (Mesylate:ab,ti AND "Dabigatran Etexilate":ab,ti) OR pradax:ab,ti OR pradaxa:ab,ti OR prazaxa:ab,ti OR rendix:ab,ti OR Apixaban:ab,ti OR eliques:ab,ti OR eliquis:ab,ti OR edoxaban:ab,ti OR endoxaban:ab,ti OR lixiana:ab,ti OR roteas:ab,ti OR savaysa:ab,ti) AND [2008-2020]/PY

[DOI: 10.47176/mjiri.36.6]

Search strategy in Cochrane

(Cost:ti OR "cost analysis":ab,ti OR (Analysis:ab,ti AND Cost:ab,ti) OR costing:ab,ti OR "Cost Comparison":ab,ti OR "health care cost":ab,ti OR cost-effectiveness:ab,ti OR "cost effectiveness":ab,ti OR cost-utility:ab,ti OR "cost utility":ab,ti OR cost-benefit:ab,ti OR "cost benefit":ab,ti OR "economic evaluation":ab,ti OR "health resource allocation":ab,ti "health economic":ab,ti OR (economic:ab,ti AND medical:ab,ti) OR pharmacoeconomic:ab,ti OR "decision analysis":ab,ti OR decision-analytic:ab,ti OR economic*:ti) AND (anticoagulant:ab,ti OR "Anticoagulation Agents":ab,ti OR (Agents:ab,ti AND Anticoagulation:ab,ti) OR "Anticoagulant Agents":ab,ti OR "Anticoagulant Drugs":ab,ti OR (Drugs :ab,ti AND Anticoagulant:ab,ti) OR "DOAC":ab,ti OR "NOAC":ab,ti OR "Indirect Thrombin Inhibitors":ab,ti OR (Inhibitors:ab,ti AND Indirect Thrombin:ab,ti) OR (Thrombin Inhibitors:ab,ti AND Indirect:ab,ti) OR Rivaroxaban:ab,ti OR Xarelto:ab,ti OR Warfarin:ab,ti OR Apo-Warfarin:ab,ti OR Aldocumar:ab,ti OR Gen-Warfarin:ab,ti OR Warfant:ab,ti OR Coumadin:ab,ti OR Marevan:ab,ti OR "Warfarin Potassium":ab,ti OR (Potassium:ab,ti AND Warfarin:ab,ti) OR "Warfarin Sodium":ab,ti OR (Sodium:ab,ti AND Warfarin:ab,ti) OR Coumadine:ab,ti OR Tedicumar:ab,ti OR dabigatran:ab,ti OR Pradaxa:ab,ti OR "Dabigatran Etexilate":ab,ti OR (Etexilate:ab,ti AND Dabigatran:ab,ti) OR "Dabigatran Etexilate Mesylate":ab,ti OR ("Etexilate Mesylate":ab,ti AND Dabigatran:ab,ti) OR (Mesylate:ab,ti AND "Dabigatran Etexilate":ab,ti) OR pradax:ab,ti OR pradaxa:ab,ti OR prazaxa:ab,ti OR rendix:ab,ti OR Apixaban:ab,ti OR eliques:ab,ti OR eliquis:ab,ti OR edoxaban:ab,ti OR endoxaban:ab,ti OR lixiana:ab,ti OR roteas:ab,ti OR savaysa:ab,ti) AND [2008-2020]/PY

Search strategy in National Health Service Economic Evaluation Database (NHS EEDS)

(Cost OR "cost analysis" OR (Analysis AND Cost) OR costing OR "Cost Comparison" OR "health care cost" OR cost-effectiveness OR "cost effectiveness" OR cost-utility OR "cost utility" OR cost-benefit OR "cost benefit" OR "economic evaluation" OR "health resource allocation" OR "health economic" OR (economic AND medical) OR pharmacoeconomic OR "decision analysis" OR decision-analytic OR economic*) AND (anticoagulant OR "Anticoagulation Agents" OR (Agents AND Anticoagulation) OR "Anticoagulant Agents" OR "Anticoagulant Drugs" OR (Drugs AND Anticoagulant) OR "DOAC" OR "NOAC" OR "Indirect Thrombin Inhibitors" OR (Inhibitors AND Indirect Thrombin) OR (Thrombin Inhibitors AND Indirect) OR Rivaroxaban OR Xarelto OR Warfarin OR Apo-Warfarin OR Aldocumar OR Gen-Warfarin OR Warfant OR Coumadin OR Marevan OR "Warfarin Potassium" OR (Potassium AND Warfarin) OR "Warfarin Sodium" OR (Sodium AND Warfarin) OR Coumadine OR Tedicumar OR dabigatran OR Pradaxa OR "Dabigatran Etexilate" OR (Etexilate AND Dabigatran) OR "Dabigatran Etexilate Mesylate" OR ("Etexilate Mesylate" AND Dabigatran) OR (Mesylate AND "Dabigatran Etexilate") OR pradax OR pradaxa OR prazaxa OR rendix OR Apixaban OR eliques OR eliquis OR edoxaban OR endoxaban OR lixiana OR roteas OR savaysa)

Appendix S2. Low and middle income countries

Low-income economies ($1,035 or less)	Afghanistan, Guinea-Bissau, Sierra Leone, Burkina Faso, Haiti, Somalia, Burundi, Korea, Dem. People's Rep., South Sudan, Central African Republic, Liberia, Sudan, Chad, Madagascar, Syrian Arab Republic, Congo, Dem. Rep, Malawi, Tajikistan, Eritrea, Mali, Togo, Ethiopia, Mozambique, Uganda, Gambia, The, Niger, Yemen, Rep, Guinea, Rwanda
Lower-middle income economies ($1,036 to $4,045)	Angola, Honduras, Papua New Guinea, Algeria, India, Philippines, Bangladesh, Kenya, São Tomé and Principe, Benin, Kiribati, Senegal, Bhutan, Kyrgyz Republic, Solomon Islands, Bolivia, Lao PDR, Sri Lanka, Cabo Verde, Lesotho, Tanzania, Cambodia, Mauritania, Timor-Leste, Cameroon, Micronesia, Fed. Sts., Tunisia Comoros, Moldova, Ukraine, Congo, Rep., Mongolia, Uzbekistan, Côte d'Ivoire, Morocco, Vanuatu, Djibouti, Myanmar, Vietnam, Egypt, Arab Rep., Nepal, West Bank and Gaza, El Salvador, Nicaragua, Zambia, Eswatini, Nigeria, Zimbabwe, Ghana, Pakistan
Upper-middle-income economies ($4,046 to $12,535)	Albania, Fiji, Montenegro, American Samoa, Gabon, Namibia, Argentina, Georgia, North Macedonia, Armenia, Grenada, Paraguay, Azerbaijan, Guatemala, Peru, Belarus, Guyana, Russian Federation, Belize, Indonesia, Samoa, Bosnia and Herzegovina, Iran, Islamic Rep., Serbia, Botswana, Iraq, South Africa, Brazil, Jamaica,St. Lucia, Bulgaria, Jordan, St. Vincent and the Grenadines, China, Kazakhstan, Suriname, Colombia, Kosovo, Thailand, Costa Rica, Lebanon, Tonga, Cuba, Libya, Turkey, Dominica, Malaysia, Turkmenistan, Dominican Republic, Maldives, Tuvalu, Equatorial Guinea, Marshall Islands, Venezuela, RB, Ecuador, Mexico

Source: World bank

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