PharmacoEconomics (2023) 41:913–943
https://doi.org/10.1007/s40273-023-01276-5

SYSTEMATIC REVIEW

Cost Effectiveness of Strategies to Manage Atrial Fibrillation in Middle- and High-Income Countries: A Systematic Review

Charles Okafor[1,2] · Joshua Byrnes[1,2] · Simon Stewart[2,3] · Paul Scuffham[1,2] · Clifford Afoakwah[1,2]

Accepted: 18 April 2023 / Published online: 19 May 2023

Abstract

Background Atrial fibrillation (AF) remains the most common form of cardiac arrhythmia. Management of AF aims to reduce the risk of stroke, heart failure and premature mortality via rate or rhythm control. This study aimed to review the literature on the cost effectiveness of treatment strategies to manage AF among adults living in low-, middle- and high-income countries.

Methods We searched MEDLINE (OvidSp), Embase, Web of Science, Cochrane Library, EconLit and Google Scholar for relevant studies between September 2022 and November 2022. The search strategy involved medical subject headings or related text words. Data management and selection was performed using EndNote library. The titles and abstracts were screened followed by eligibility assessment of full texts. Selection, assessment of the risk of bias within the studies, and data extraction were conducted by two independent reviewers. The cost-effectiveness results were synthesised narratively. The analysis was performed using Microsoft Excel 365. The incremental cost effectiveness ratio for each study was adjusted to 2021 USD values.

Results Fifty studies were included in the analysis after selection and risk of bias assessment. In high-income countries, apixaban was predominantly cost effective for stroke prevention in patients at low and moderate risk of stroke, while left atrial appendage closure (LAAC) was cost effective in patients at high risk of stroke. Propranolol was the cost-effective choice for rate control, while catheter ablation and the convergent procedure were cost-effective strategies in patients with paroxysmal and persistent AF, respectively. Among the anti-arrhythmic drugs, sotalol was the cost-effective strategy for rhythm control. In middle-income countries, apixaban was the cost-effective choice for stroke prevention in patients at low and moderate risk of stroke while high-dose edoxaban was cost effective in patients at high risk of stroke. Radiofrequency catheter ablation was the cost-effective option in rhythm control. No data were available for low-income countries.

Conclusion This systematic review has shown that there are several cost-effective strategies to manage AF in different resource settings. However, the decision to use any strategy should be guided by objective clinical and economic evidence supported by sound clinical judgement.

Registration CRD42022360590.

1 Introduction

Among the cardiac arrhythmias, atrial fibrillation (AF) remains the most common from a public health to clinical perspective [1]. In 2019, approximately 57.9 million people worldwide had AF, twice the number in 1990 [2], representing about 1% of the general population aged 18 years and above. Over 30% of hospital admissions for cardiac rhythm problems were due to AF [3]. AF independently confers a significant long-term risk for ischaemic stroke (fivefold), acute coronary events (including myocardial infarction) and the syndrome heart failure (HF) [1]. Independent of these deadly and disabling conditions, AF is associated with impaired quality of life and premature mortality [3, 4]. Within the progressively ageing populations of high-income countries in whom the antecedents for AF remain high (particularly hypertension), the burden AF is progressively increasing [1]. Although incident AF is closely related to older age, in low- and middle-income countries (LMIC) where hypertension remains largely undetected and uncontrolled, the future burden of AF is also likely to rise [5]. The management of this disease is also abysmal in LMIC due to poor access to healthcare [5].

The management of AF is usually individualised and dependent on several factors including patient factors (e.g. risk of a particular therapy for a patient, patient's overall risk

Extended author information available on the last page of the article

Key Points for Decision Makers

Apixaban, left atrial appendage closure, propranolol, catheter ablation and convergent procedures are potentially efficient to manage atrial fibrillation in high-income countries. Apixaban, warfarin and radiofrequency catheter ablation are potentially efficient to manage atrial fibrillation in middle-income countries.

More population-specific clinical trials, head-to-head trials and other relevant population-specific studies are needed to provide more robust data for economic evaluation, which will in turn support decision making.

The decision to use any treatment strategy should always be individualised and guided by strong objective clinical and economic evidence and sound clinical judgement.

of stroke and other emboli-related problems) and diagnostic factors (e.g. severity of symptoms and the cause or duration of AF). In general, the short-term goals for the management of AF include symptom relief, and prevention of AF-associated complications including acute decompensated heart failure (HF) in those with impaired systolic function [1]. In the longer-term, key goals include the prevention of stroke, symptom relief, heart rate control, rhythm control and aggressive risk factors management [1]. Prevention of (ischaemic) stroke remains the principal goal in the management of most AF patients, although there is increasing focus on the prevention of chronic HF; particularly as HF begets AF and vice versa [6]. To date, randomised controlled trials (RCTs) do not suggest the superiority of rate control over rhythm control to achieve a normal rhythm. However, if the ultimate goal is restoration and maintenance of sinus rhythm, rate control medication is usually continued throughout the follow-up, unless continuous sinus rhythm is present. Managing AF-related abnormal heart rate may also control abnormal rhythm, but in some cases, cardioversion or ablation procedures are required to control the abnormal rhythm. There are different management strategies for AF, so it is important to stratify the risk profile of each patient, as some patients may require earlier and different intervention from others. This led to the establishment of the $CHADS_2$ [congestive heart failure, hypertension, age $\geq$ 75 years, diabetes, stroke (doubled)] score. Recently, a new and updated version known as CHA_2DS_2-VASc [congestive heart failure, hypertension, age $\geq$ 75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 years and sex category (female)] has taken over as the most accurate risk stratification tool, offering more accurate results for low-risk patients [1].

The prevention of AF-related (ischaemic) stroke can be achieved by different intervention strategies. Anti-coagulants including Vitamin K antagonists (VKA) and Factor X_a inhibitors are the most commonly used interventions. Types of VKA that can be administered to prevent AR-related stroke include warfarin, acenocoumarol, phenprocoumon and fluindione. Historically, warfarin is the most used VKA and the mainstay of therapy when anti-coagulation is required. Modern alternatives to warfarin [due to the need for routine international normalized ratio (INR) therapeutic monitoring and high-risk of haemorrhagic strokes/other major bleeding events] are the Factor Xa inhibitors or the direct oral anticoagulants (DOAC). These include apixaban, dabigatran, edoxaban and rivaroxaban. Anti-platelets such as aspirin (a cyclooxygenase inhibitor) and, more latterly, clopidogrel (a selective adenosine diphosphate receptor inhibitor) are also used in AF but often in combination with anti-coagulants. In patients with AF from mechanical heart valves, low molecular weight heparin (LMWH) or unfractionated heparin (UFH) can be used for 'bridging' anti-coagulation. Direct thrombin inhibitors such as argatroban and bivalirudin can be used as alternatives for heparin. Studies have shown that DOACs are as effective as the VKAs in preventing AF-related stroke, but in terms of cost effectiveness, VKAs still appears as an attractive strategy in resource-limited settings [7] due to the high cost of DOACs. In high-income countries, however, DOACs seem to be the new conventional strategies [8]. Anti-coagulant treatment is likely unnecessary in males with CHA_2DS_2-VASc score of 0 and females with a score of 1. Scores $\geq$ 1 for males and $\geq$ 2 for females would require anti-coagulants.

Alternatively, strategies to control heart rate associated with AF include beta-blockers (metoprolol, bisoprolol, atenolol, esmolol, propranolol, carvedilol), non-dihydropyridine calcium channel antagonists (verapamil, diltiazem), digitalis glycosides (digoxin and digitoxin) and some class 3 anti-arrhythmic drugs (amiodarone and dronedarone) [1]. The use of any of these strategies for heart rate control depends on the treatment objectives such as acute rate control or long-term rate control, and factors such as left ventricular dysfunction and failed rhythm control. Anti-arrhythmic strategies (if required) include electric cardioversion, pharmacological cardioversion (flecainide, amiodarone, sotalol, ibutilide, propafenone and vernakalant), ablation procedures which could be catheter ablation (e.g. radiofrequency, cryoballoon or hybrid ablation—convergent procedure), or surgical ablation. As mentioned earlier, the use of any strategy for rhythm control depends on several factors including the symptoms, severity of AF (according to duration and class), ventricular dysfunction and haemodynamic stability. Studies have shown that rate and rhythm control strategies can reduce cardiovascular morbidities and mortality [9, 10].

In the long term, the key goal of any AF management strategy is to improve modifiable risk factors associated with the condition including lifestyle modification, monitoring and any potential triggers of paroxysmal AF (e.g. excessive alcohol intake). However, these strategies are often considered as secondary or tertiary and are used in combination with other strategies described above [11].

While some cases of AF are paroxysmal or persistent and self-terminate in less than a year with appropriate management, most cases transit to a life-long/permanent condition. This necessitates lifetime management and monitoring of rate control to reduce the increased risk of tachycardia-induced cardiomyopathy and stroke. Although both are very costly, this raise concerns around the cost effectiveness of applied management strategies. As the cost of managing AF is becoming as important as the health outcomes, economic evaluation of treatment strategies to manage AF has become an indispensable tool to inform decision making. This systematic review answers the following research question: What strategies to manage atrial fibrillation among people aged 18 years and above were cost effective in low-, middle- and high-income countries between 2012 and 2022? The outcome of this study will guide decision making in the management of AF amidst several strategies used in different settings to manage the disease.

2 Methods

2.1 Protocol and Registration

The design of this systematic review was in accordance with the recommendation in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement [12]. Details of the PRISMA checklist are provided in Electronic Supplementary Material (ESM) 1. This review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO), CRD42022360590.

To aid the development of the study design, we did a preliminary assessment of literature using PubMed and Google Scholar to identify studies' characteristics and methodologies. This helped to define the final inclusion and exclusion criteria used for the search.

2.2 Eligibility Criteria

Studies included in this review were original research on the economic evaluation of AF management strategies. The studies presented cost data and health outcome measure(s) for patients aged 18 years and above. There was no restriction on comorbidities or co-treatment strategies. Full-text articles were included. The studies were limited to humans only, in English language and published between January 2012 and November 2022.

Economic evaluations of other arrhythmias (other than atrial fibrillation) or other cardiac diseases, reviews and commentaries, opinion papers, conference abstracts or proceedings and qualitative reports were excluded. Studies whose costs and health outcomes were estimated using proxied data were also excluded. Studies with incomplete information needed for economic evaluation, and studies that evaluated one DOAC for stroke prevention were excluded, except in the case of mixed treatment strategies. The reason for excluding studies that evaluated a single DOAC was because the four novel DOACs (apixaban, dabigatran, edoxaban and rivaroxaban) were under patency in year 2022. Hence, to eliminate analytical bias of the included studies, we included only studies that evaluated the relative efficiency of at least two DOACs in head-to-head comparisons.

2.3 Information Sources

Based on expert librarians' recommendations [13] and after an assessment of the health economic core library recommendations by the US National Library of Medicine [14], we searched MEDLINE (OvidSp), Embase, Web of Science, Cochrane Library, EconLit (EBSCOhost) and Google Scholar to identify relevant studies.

2.4 Search Strategy

The search was performed in September 2022. Related 'search terms' which include related relevant medical subject headings (MeSH), or related text words (title, abstract and keywords) were combined to form a union (concept cluster). For example, if A, B and C represent related search terms, the union was formed as 'A or B or C'. Several relevant concept clusters were created. The concept clusters were combined to form an intersection cluster. For example, if D, E and F are concept clusters, they were combined as 'D and E and F'. The results were then reviewed by looking at the MeSH, subheadings, titles and abstract to check if there are terms that could improve our search. For instance, in our preliminary search, we searched for 'atrial fibrillation' and 'arrhythmia' which present results with all related headings and subheadings and were combined to form a related MeSH 'search term'. We then searched for text words like 'arrhythmia', 'dysrhythmia', and 'abnormal heart rhythm' appearing in the title, abstract or keywords, which were combined to form related text words, (search term). Both related 'search terms' (MeSH and text words)

were combined to form a concept cluster. Details of the search strategies are shown in ESM 2. The MEDLINE search strategy was adapted for search in other databases. Auto-alert systems was set up to provide literature updates while the data extraction and analyses are ongoing. The auto-alert systems were stopped 2 months after the data extraction (November 2022).

2.5 Data Management and Selection Process

All searched results from the six databases were exported into a single EndNote library. A union group was created to contain all the articles from the different databases. De-duplication of studies was performed with EndNote. From the union group, different subgroups to represent exclusion criteria were created. Excluded studies were exported to different exclusion 'group set' based on the criteria for exclusion. A study that does not meet the inclusion criteria for multiple reasons was exported to the relevant exclusion 'group set' in the order of priority: 'subject area', 'originality', 'economic evaluation' and 'clarity' completeness, 'study from 2012 and beyond', and more than one DOAC evaluated (in the case of stroke prevention) (see ESM 2).

Selection was performed independently by two reviewers (C.O. and C.A.). A third reviewer (J.B.) overviewed the selections by the first two reviewers and resolved any selection disagreement among the first two reviewers. First, titles were screened followed by the abstracts of original research articles that involve the economic evaluation of atrial fibrillation management strategies. Next, an auto search for the full text of the articles whose abstracts were eligible was initiated. The full text of the potential articles was assessed for costs, health outcomes and clarity of reporting.

2.6 Data Collection Process

An electronic data extraction form was used. Two reviewers (C.O. and C.A.) independently extracted and managed the data from the included studies. Disagreement with the extraction results from the two reviewers that cannot be resolved by them was resolved by the third reviewer (J.B.). The data was collected based on the 2022 International Society for Pharmacoeconomics and Outcome Research (ISPOR) Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline [15] (see ESM 2).

2.7 Data Items, Outcomes and Prioritisation

Data was extracted based on the following:

(a) Publication: title, authors, year, study objectives, sample size, gender, setting/country the study was conducted, etc.

(b) Study design: randomised-control trials, cohort studies, case-control studies, cross-sectional studies, type of economic evaluation, time horizon, type of atrial fibrillation, comparators, risk of stroke based on the CHA_2DS_2-VASc score, etc. A CHA_2DS_2-VASc score of 0 is 'low' risk of stroke, 1 is 'moderate' and any score above 1 is a 'high' risk.

(c) Cost and outcome measures: cost perspective, quality-adjusted life-years (QALY), discount rate, willingness-to-pay threshold, price year and currency, etc.

(d) Other relevant information, e.g. study assumptions.

2.8 Risk of Bias Assessment

Risk of bias assessment of the individual studies was done at the outcome level using the Consensus Health Economic Criteria (CHEC) checklist designed for conducting economic evaluation-based systematic reviews [16]. This checklist has 19 reporting standards for economic model characteristics, identification and valuation of costs and outcomes, discussion section, conclusions as well as funding and conflicts of interest statement. As the risk of bias tool did not provide thresholds to include or exclude studies for data synthesis, an internally created conservative classification system was used to ensure that only studies with low risk to moderate risk of bias were included in the synthesis. The risk of bias in this scenario was defined as the inappropriateness or failure of a study to conduct or report the applicable items indicated on the risk of bias tool. The risk of bias was measured as a percentage of the failure or inappropriateness. Studies were classified as 'low risk' (0–10%), 'moderate risk' (11–30%), or 'high risk' (> 30%) based on the percentage of applicable items for each study which were not reported or inappropriately reported. Studies with high risk of bias were excluded from the data synthesis. The checklist was completed in duplicate by two members of the review team (C.O. and C.A.). Differences were resolved with the third author (J.B.). Details of the risk of bias assessment is available in the supplementary file 3 (ESM 3).

2.9 Data Synthesis

A narrative synthesis and summary of answers to the research question was performed due to heterogeneities in the identified studies. Such heterogenies emanated from either difference in country's economic development or treatment goals for managing AF. Hence, the grouping of studies for narrative synthesis was first based on the income level classification by the World Bank [high-income countries (HIC), middle-income countries (MIC) and low-income countries (LIC)]. Studies were then grouped as per the treatment goals including stroke prevention, rate control and

rhythm control. The analysis was performed using Microsoft Excel 365 (Microsoft, Seattle, USA). The ICER for each study was adjusted to 2021 USD value following the guidelines of the Campbell and Cochrane Economics Methods Group (CCEGM) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) [17].

3 Results

3.1 Screening and Selection of Studies

A total of 2019 articles were identified from five databases (Medline, 221; Embase, 1108; Web of Science, 518; Cochrane, 102 and EconLit, 9) and Google Scholar (61 articles). Two potential articles from Medline were identified through the auto alert system but were duplicates. After de-duplication, 1803 articles were available for screening. The studies excluded at the screening phase were moved to exclusion 'group sets' based on the reason for exclusion in a hierarchy order described in the methodology. A total of 230 potential articles were available for eligibility check after phase 1 screening. Conference abstracts and studies which had multiple, relevant missing information for economic evaluation were excluded as 'incomplete information' studies, while studies with unspecific methodology or analytical approach were excluded as 'not specific' studies. At the end of the eligibility assessment, a total of 50 studies met the inclusion criteria. Figure 1 describes the flow diagram of the selection process. The EndNote library (available upon request) summarises the reasons for exclusion of studies.

3.2 Characteristics of the Included Studies

Data were extracted from the included studies as per the data items described in the methodology. All studies were for patients with non-valvular AF. No study was found to evaluate the management strategies of AF in LIC setting. For stroke prevention strategies, 32 studies evaluated the cost effectiveness in HIC [8, 18–48], while seven studies evaluated the cost effectiveness in MIC [49–55]. Ten studies in HIC [10, 28, 29, 56–62] and three studies in MIC [63–65] evaluated the cost effectiveness of rhythm control strategies. Only one study [10] evaluated the cost effectiveness of rate control strategies in AF management in HIC. Of the 32 studies that evaluated strategies for stroke prevention in HIC, 14 were from North America [8, 25, 26, 28, 29, 31, 32, 37–39, 44, 46–48], 13 from Europe [18, 19, 22–24, 27, 30, 33–35, 40, 42, 45], 4 from Asia [21, 29, 43, 47] and 1 from Oceania [28]. The proportion of male sex (52–77%) was higher than the female sex in most of the studies. Five studies from Asia [10, 29, 63–65], four from North America [56–59], two from Oceania [28, 61] and two from Europe [60, 62], respectively evaluated management strategies for rhythm control.

All the studies were cost-utility analyses with QALY as the main outcome measure. All studies were cohort studies with most studies designed using a lifetime horizon. Few studies had a 5-year and 10-year time horizon [28, 29, 45, 52, 57, 61, 65]. Markov models were the principal type of model employed in the assessment of included studies. The design of the model varied across the studies with health states range from 8 to 17 health states. The payer perspective was the most applied costing perspective (68% of the studies), while 24% and 12% of the studies were performed from the provider perspective [20, 23, 25, 33, 34, 36, 43, 47, 55, 58, 61, 64] and societal perspective [10, 19, 23, 31, 51, 53], respectively. Most of the studies (59%) applied an annual discount rate of 3% for both costs and outcomes. Twenty-four per cent of studies applied 3.5% discount rate for both costs and outcomes. Twelve per cent of the studies applied 5% as discount rate for both costs and outcomes, while the remaining studies applied a discount rate of 1.5% for outcomes, and 4% or 4.5% for costs. The willingness-to-pay threshold also varied across the studies. Studies from the USA used a threshold of either $50,000 [25, 28, 38, 39, 46, 47] or $100,000 [8, 19, 26, 39, 58] per QALY gained. Studies from the UK used the National Institute of Health and Clinical Excellence (NICE) recommended threshold between £20,000 and £30,000 per QALY [40, 60, 62]. Other studies in Europe adopted the NICE recommendation but expressed values in Euros or US$ [18, 19, 22–24, 27, 30, 34, 35, 40, 42, 45]. Some other studies used government-led guidelines [22, 34, 44], or one to three times the gross domestic product per capita (GDP) of the country citing the World Health Organization [10, 21, 43, 47, 56]. The sample size was hypothetical for most studies, between 1000 and 10,000 patients, while some studies used the sample size from observational data repository or randomised-control trials, with sample sizes ranging from 231 to 212,459 patients [10, 21, 34, 42, 50, 54, 56, 58, 61, 65]. The patients average age was 67 (55–78) years (see Table 1).

Identifying the optimal stroke prevention strategy was the predominant objective of most of the included studies. Evaluated interventions for stroke prevention include warfarin, aspirin, clopidogrel, LMWH, the DOACs (apixaban, dabigatran, rivaroxaban and edoxaban) and left atrial appendage closure (LAAC). Strategies for rhythm control identified in the studies include anti-arrhythmic drugs (atenolol, sotalol, pilsicainide, flecainide, propafenone, dronedarone and amiodarone); catheter ablation, including cryoballoon ablation, radiofrequency catheter ablation (RFCA) and hybrid procedure (convergent procedure). The only study that evaluated a rate control strategy assessed atenolol, propranolol, betaxolol, bevantolol, bisoprolol, diltiazem and verapamil.

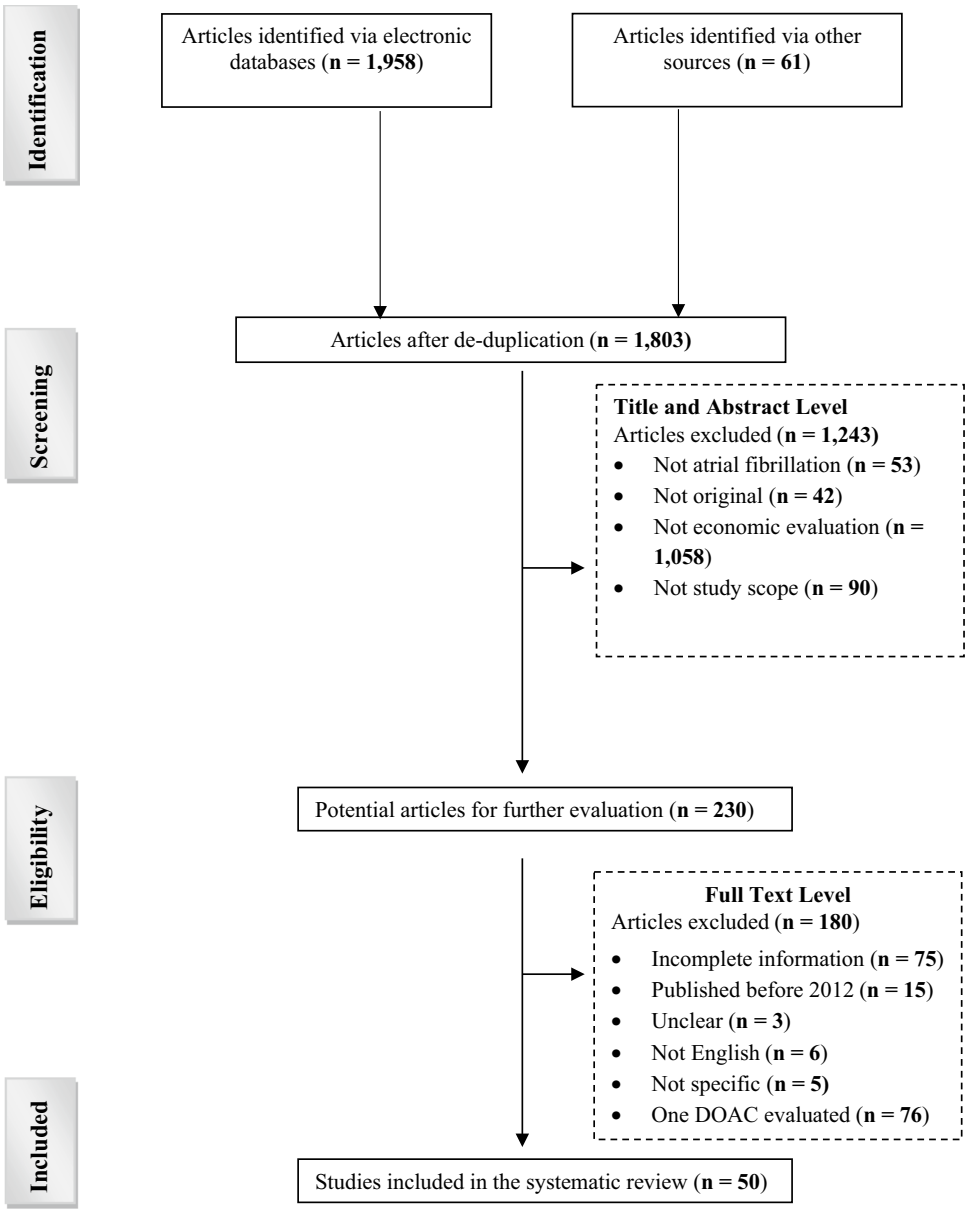

Fig. 1 PRISMA flowchart of the study selection process

3.3 Risk of Bias Assessment

The risk of bias assessment performed using the CHEC list (available in ESM 3) showed that the included studies had low to moderate risk of bias. This was partly due to preliminary assessment done during the studies selection with EndNote library.

3.4 Cost Effectiveness of Treatment Strategies

3.4.1 Stroke Prevention Strategies in High-Income Countries

In patients at low risk of stroke, three out of six studies showed that apixaban was the optimal choice to prevent stroke [30, 37, 40]. These three studies compared warfarin with different DOACs only. Only one study compared warfarin with DOACs, LAAC, clopidogrel and aspirin, and it showed that LAAC was the optimal strategy [33]. Dabigatran was the optimal choice specifically from one study [40], likewise rivaroxaban [43]. Pharmacogenomic-guided warfarin (PG-warfarin) was cost effective when compared with standard warfarin care [41].

In those at moderate risk of stroke, apixaban was the optimal strategy in 11 of 18 included studies [8, 18, 26, 27, 29, 35, 37, 41, 43, 45, 47]. These studies either compared warfarin with DOACs or compared between DOACs, but 1 of the 11 studies compared LAAC with warfarin and DOACs [34]. Dabigatran was the optimal choice in three studies [22, 37, 48], while rivaroxaban [20], edoxaban

Table 1 Characteristics of included studies

Author, year and reference	Country	Study perspective	Age (years)	Sex proportion	Key assumptions	Treatment strategy	Time horizon	Base-case intervention	Comparator	Discount rate
Khaykin et al., 2015 [56]	Canada (HIC)	Payer	55	M and F	Patients in ablation arm assumed to have failure with first-line AAD; patients may have a maximum of three ablation; failure of third ablation would require second-line AAD	Rhythm control	Lifetime; 10 and 5 year	AAD	CA	5%
Anderson et al., 2014 [57]	USA (HIC)	Payer	60	M and F	70% of patients would accept the second CA, 40% the third and 35% the fourth. 30% will accept second convergent procedure	Rhythm control	5 year	AAD	Convergent procedure; CA	3%
Athanasakis et al., 2015 [18]	Greece (HIC)	Payer	70	M (65%) and F (35%)	Risk adjustment for ischaemic stroke and MI	Stroke prevention	Lifetime	Apixaban	Dabigatran; rivaroxaban	3%
Canestaro et al., 2013 [19]	USA (HIC)	Societal	70	M and F	Treatment with warfarin resulted in a 64% reduction in clinical events	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; rivaroxaban	3%
Cervantes et al., 2022 [20]	Spain (HIC)	Payer	73	M (52%) and F (48%)	Patients can switch between DOAC and Vitamin K antagonist	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; rivaroxaban	3%
Chew et al., 2022 [58]	USA (HIC)	Provider	68	M (63%) and F (37%)	Use of the 2017 US lifetable to calibrate survival beyond 82 years	Rhythm control	Lifetime	AAD	Catheter ablation	3%

Table 1 (continued)

Author, year and reference	Country	Study perspective	Age (years)	Sex proportion	Key assumptions	Treatment strategy	Time horizon	Base-case intervention	Comparator	Discount rate
Choi et al., 2022 [21]	South Korea (HIC)	Provider	≥ 18	M and F	All health events, except for GI bleeding, were assumed to remain in the post-disease state or to transition to the death state	Stroke prevention	20 year	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	4.5%
Coyle et al., 2013 [22]	Canada (HIC)	Payer	72	M and F	Cost of apixaban was assumed to be same cost as dabigatran because there was no cost data for the former at the time of the study	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; rivaroxaban	5%
de Jong et al., 2019 [23]	The Netherlands (HIC)	Societal	74	M (54%) and F (46%)	Patients who experienced a non-fatal haemorrhagic stroke or non-fatal MI were assumed to discontinue their AC therapy permanently and were assigned acute and long-term maintenance costs	Stroke prevention	Lifetime	Apixaban	Warfarin; dabigatran; edoxaban; rivaroxaban	4% (costs) and 1.5% (outcomes)
Dilokthornsakul et al., 2020 [51]	Thailand (MIC)	Societal	68	M and F	The mortality of patients with AF without any complication was assumed to be equal to that of the general Thai population	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	3%

Table 1 (continued)

Author, year and reference	Country	Study perspective	Age (years)	Sex proportion	Key assumptions	Treatment strategy	Time horizon	Base-case intervention	Comparator	Discount rate
Du et al., 2019 [63]	China (MIC)	Payer	≥ 60	M (50%) and F (50%)	Assumed an equal percentage of patients with paroxysmal and persistent AF	Rhythm control	8, 15 and 20 year	AAD	CA	3.5%
Freeman et al., 2016 [24]	USA (HIC)	Payer	70	M and F	Accounted for the temporary decrease in quality of life associated with the LAAC procedure by reducing quality of life by 30% for 10 days	Stroke prevention	Lifetime	LAAC	Dabigatran; warfarin	3%
Harrington et al., 2013 [25]	USA (HIC)	Provider	70	M and F	Used UK price for Apixaban	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; rivaroxaban	3%
Hospodar et al., 2018 [26]	USA (HIC)	Payer	65	N/a	Acute costs of events were assumed to be the same for all treatments	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	3%
Hu et al., 2022 [64]	China (MIC)	Provider	55	M (60%) and F (40%)	No restrictions were set for the order of events or the intervals between events	Rhythm control	Lifetime	AAD	STAI (RFA); CB2	3.5%
Janzic and Kos, 2015 [27]	Slovenia (HIC)	Payer	70	N/a	Consequences of clinical events (e.g., disability level, death) were assumed to be independent of the treatment strategy	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	3%

Table 1 (continued)

Author, year and reference	Country	Study perspective	Age (years)	Sex proportion	Key assumptions	Treatment strategy	Time horizon	Base-case intervention	Comparator	Discount rate
Kawakami et al., 2021 [28]	Australia (HIC)	Provider	65	M and F	Assumed that a transoesophageal echocardiography and a transthoracic echocardiogram (TTE) would be performed before AF ablation in all patients, and a follow-up TEE after LAAC	Rhythm control plus Stroke prevention	10 year	CA + OAC	CA + LAAC	3%
Kim et al., 2019 [10]	South Korea (HIC)	Societal	≥ 18	N/a	Assumed drug usage or compliance is the same	Rate control and rhythm control	20 year	Atenolol	Propranolol; betaxolol; bevantolol; bisoprolol; diltiazem; verapamil	3%
Kimura et al., 2017 [29]	Japan (HIC)	Payer	60	N/a	The monthly probability of death from stroke was set at 5.61% per month during the first 12 months after stroke onset and 1.43% per month thereafter	Rhythm control plus stroke prevention	10 year	CA + warfarin	CA + dabigatran	3%
Kongnakorn et al., 2015 [30]	Belgium (HIC)	Payer	≥ 18	N/a	Segregation between ischaemic stroke, ICH and systemic embolism	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; rivaroxaban	3.5% (costs) and 1.5% (outcomes)

Table 1 (continued)

Author, year and reference	Country	Study perspective	Age (years)	Sex proportion	Key assumptions	Treatment strategy	Time horizon	Base-case intervention	Comparator	Discount rate
Labori et al., 2022 [31]	Sweden (HIC)	Provider; societal	74	M and F	Standard error calculated by assuming a statistical range of ± 20% around the base case value equals the confidence interval	Stroke prevention	Lifetime	Std of care	LAAC	3%
Lanitis et al., 2014 [32]	France (HIC)	Payer	> 18	N/a	N/a	Stroke prevention	Lifetime	Warfarin	Apixaban; Aspirin; dabigatran; edoxaban; rivaroxaban	4%
Lau et al., 2021 [59]	Canada (HIC)	Payer	65	M and F	Assumed no CA- specific effect on health utility for base case, apart from decrements attributable to outcomes or complications.	Rhythm control	Lifetime	AAD	CA	3%
Lee et al., 2016 [33]	USA (HIC)	Provider	65	M and F	Assumed the bleeding rate in the first year after LAAC was lower than warfarin or clopidogrel plus aspirin	Stroke prevention	Lifetime	Warfarin	Aspirin; clopidogrel + aspirin; LAAC; dabigatran; apixaban; rivaroxaban	3%

Table 1 (continued)

Author, year and reference	Country	Study perspective	Age (years)	Sex proportion	Key assumptions	Treatment strategy	Time horizon	Base-case intervention	Comparator	Discount rate
Leung et al., 2022 [60]	UK (HIC)	Payer	64	M (66%) and F (33%)	Non-vitamin K antagonist products (e.g. Pradaxa, Eliquis, Xarelto and Lixiana) were assumed to account for 74% of patients on OACs, with the remainder on Warfarin (with monitoring)	Rhythm control	Lifetime	AAD	CA	3.5%
Liao et al., 2020 [49]	China (MIC)	Payer	65	N/a	The dose of anticoagulants was assumed not to need adjustment by age	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	3%
Liu and Chen, 2017 [50]	China (MIC)	Payer	76	M (56%) and F (44%)	Assumed that the risk of stroke would increase by 1.4-fold per 10 years of life, and that the risk of mortality increased by 3.7-fold after an ischaemic stroke or ICH	Stroke prevention	Lifetime	Apixaban	Dabigatran; warfarin; rivaroxaban	3.5%
Mendoza et al., 2019 [52]	Colombia (MIC)	Payer	> 18	N/a	N/a	Stroke prevention	10 year	Apixaban	Dabigatran; warfarin; rivaroxaban	3%

Table 1 (continued)

Author, year and reference	Country	Study perspective	Age (years)	Sex proportion	Key assumptions	Treatment strategy	Time horizon	Base-case intervention	Comparator	Discount rate
Micieli et al., 2016 [34]	Canada (HIC)	Payer	≥ 18	N/a	The utility decrements for rivaroxaban and apixaban were assumed to be the same as dabigatran. As no quality-of-life estimates for LAAC exists, it was assumed that the utility decrement is similar to coronary angioplasty, a procedure quite similar to LAAC	Stroke prevention	Lifetime	LAAC	Apixaban; dabigatran; warfarin; rivaroxaban	5%
Pathak et al., 2017 [61]	Australia (HIC)	Provider	59	M (66%) and F (33%)	Patient would achieve 'AF freedom' at year 4	Rhythm control	10 year	No RFM	RFM	3%
Pradelli et al., 2014 [35]	Italy (HIC)	Payer	70	M (65%) and F (35%)	Where 95% CI was unavailable from the original data, it has been calculated assuming a SEM equaling 25% of the mean	Stroke prevention	Lifetime	Apixaban	Dabigatran; rivaroxaban	3.5%
Rattanachotphanitet al., 2019 [53]	Thailand (MIC)	Societal; payer	68	M and F	Limits in parameter variation were based on 95% confidence intervals of the point estimates and otherwise on ± 20%.	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	3%

Table 1 (continued)

Author, year and reference	Country	Study perspective	Age (years)	Sex proportion	Key assumptions	Treatment strategy	Time horizon	Base-case intervention	Comparator	Discount rate
Reddy et al., 2018 [36]	USA (HIC)	Payer	70	M and F	Patients who discontinued primary drug therapy were assumed to switch to aspirin. Discontinuation of second-line therapy was assumed to result in no treatment	Stroke prevention	10 year; lifetime	LAAC	Warfarin; apixaban; dabigatran	3%
Reynolds et al., 2014 [62]	UK (HIC)	Payer	57	M (77%) and F (23%)	Upon first recurrence of AF, the patients were assumed to commence their first AAD (propafenone); a subsequent recurrence of AF then led to them being treated with sotalol, followed by amiodarone, and finally, rate control therapy alone (assumed to be metoprolol)	Rhythm control	Lifetime	AAD	Cryoballoon ablation	3.5%
Rognoni et al., 2014 [37]	Italy (HIC)	Payer	71	M and F	It was assumed that if anticoagulation was interrupted due to ICH or major extracranial bleeding, it would be restarted after 1 month	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; rivaroxaban	3.5%

Table 1 (continued)

Author, year and reference	Country	Study perspective	Age (years)	Sex proportion	Key assumptions	Treatment strategy	Time horizon	Base-case intervention	Comparator	Discount rate
Saw et al., 2016 [38]	Canada (HIC)	Payer	74	M (42%) and F (58%)	Patients who underwent LAAC were treated with dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for 1 month, followed by aspirin alone beyond 1 month	Stroke prevention	Lifetime	Aspirin	LAAC	5%
Shah et al., 2016 [8]	USA (HIC)	Payer	65	M and F	It was assumed that 28% of all the ischaemic strokes were transient ischaemic attacks, and the remaining could be one of four types: reversible, major, minor or fatal	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	3%
Sun et al., 2021 [54]	China (MIC)	Payer	59	M and F	To calculate the dosage of LMWH and warfarin, the study assumed a typical patient weighed 60 kg	Stroke prevention	Lifetime	LMWH + VKA	Apixaban; dabigatran; rivaroxaban	3%

Table 1 (continued)

Author, year and reference	Country	Study perspective	Age (years)	Sex proportion	Key assumptions	Treatment strategy	Time horizon	Base-case intervention	Comparator	Discount rate
Sun et al., 2019 [65]	China (MIC)	Payer	60	M and F	It was assumed that the annual poststroke, post-ICH, and post-MI treatment costs were one-tenth of the cost of immediate treatment of stroke, ICH and MI, respectively	Rhythm control	10 year	Cryoballoon ablation	RFCA	3.5%
Vargas et al., 2018 [39]	USA (HIC)	Payer	70	M and F	Despite not being an accepted treatment for stroke prevention in elderly patients with AD, aspirin remains widely used in patients with dementia. For this reason, aspirin (antiplatelet) was considered as an alternative in a secondary analysis only	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	3%
Verhoef et al., 2014 [40]	The Netherlands and UK (HIC)	Provider	70	N/a	Patients receiving either one of the new oral anticoagulants or coumarin therapy were assumed to switch to aspirin after an ICH	Stroke prevention	Lifetime	Coumarin derivative	Apixaban; dabigatran; rivaroxaban	3.5% (UK); 4% and 1.5% (costs and outcome) for the Netherlands

Table 1 (continued)

Author, year and reference	Country	Study perspective	Age (years)	Sex proportion	Key assumptions	Treatment strategy	Time horizon	Base-case intervention	Comparator	Discount rate
Verhoef et al., 2016 [41]	UK and Sweden (HIC)	Provider	71 (UK); 73 (Sweden)	N/a	Patients with a stroke had a 10% chance of dying and a 47% chance of disability, while patients with a transient ischaemic attack were assumed to fully recover	Stroke prevention	Lifetime	Std of care	PG-warfarin	3.5% (UK); 3% (Sweden)
Walter et al., 2021 [42]	Austria (HIC)	Payer	70	N/a	The model includes a discontinuation rate for anticoagulants. The discontinuation rate increases over time. An adherence rate of 90% was used for the first year	Stroke prevention	Lifetime	Apixaban	Warfarin; dabigatran; edoxaban; rivaroxaban	5%
Wang et al., 2014 [43]	Singapore (HIC)	Provider	65	N/a	Patients with an ICH or major ECH were assumed to stop anticoagulation and resume the same anticoagulant after 1 month.	Stroke prevention	Lifetime	Warfarin	Dabigatran; rivaroxaban	3%
Wong et al., 2020 [44]	Canada (HIC)	Payer	78	M (49%) and F (51%)	Patients were assumed to be adherent to the study medication, with no discontinuation	Stroke prevention	Lifetime	Aspirin	Apixaban; dabigatran; edoxaban; rivaroxaban; warfarin	1.5%

Table 1 (continued)

Author, year and reference	Country	Study perspective	Age (years)	Sex proportion	Key assumptions	Treatment strategy	Time horizon	Base-case intervention	Comparator	Discount rate
Wu et al., 2021 [45]	USA (HIC)	Payer	75	N/a	Anticoagulant therapies were assumed to cause slight derogation of the health utilities, which were assessed to be from −0.002 to −0.03 for DOACs, warfarin and aspirin, respectively	Stroke prevention	10 year	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	3%
You Joyce, 2015 [46]	USA (HIC)	Payer	65	N/a	Those who experienced a major thromboembolic event on warfarin would change to DOAC therapy	Stroke prevention	Lifetime	Genotype-guided DOAC	Universal use of DAOC	3%
Zhao et al., 2016 [47]	Singapore (HIC)	Payer	74	M and F	For cost data with no range provided, a range of variation at ± 25% was assumed. Patients with major IS or major ICH on anti-coagulant were assumed to stop treatment or switch to low-dose aspirin	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	3%

Table 1 (continued)

Author, year and reference	Country	Study perspective	Age (years)	Sex proportion	Key assumptions	Treatment strategy	Time horizon	Base-case intervention	Comparator	Discount rate
Zheng et al., 2014 [48]	UK (HIC)	Payer	71	M (64%) and F (36%)	All patients who discontinued anticoagulant therapy for other reasons were assumed to switch to aspirin, and patients who discontinued aspirin therapy were assumed to permanently discontinue all treatment	Stroke prevention	Lifetime	Dabigatran	Apixaban; warfarin; rivaroxaban	3.5%
Zhou et al., 2022 [55]	China (MIC)	Provider	≥ 18	N/a	Patients with major IS or major ICH on anticoagulant were assumed to stop treatment or switch to low-dose aspirin	Stroke prevention	Lifetime	Warfarin	Apixaban; dabigatran; rivaroxaban	5%

AAD anti-arrhythmic drug, *AD* Alzheimer's disease, *CA* catheter ablation, *ECH* extracranial haemorrhage, *F* female, *ICH* intracranial haemorrhage, *LAAC* left atrial appendage closure, *LMWH* low molecular weight heparin, *M* male, *MI* myocardial infarction, *OAC* oral anti-coagulant, *RFM* risk factor management

[39], PG-warfarin [27] and LAAC [24], were the optimal strategies in four different studies.

In those at high risk of stroke, LAAC was the optimal strategy in three of nine studies [31, 36, 38]. Two studies provided evidence that apixaban was the optimal studies, but LAAC was not a comparator in any of the two studies [32, 37]. PG-warfarin and PG-DOAC were the cost-effective choice in two different studies, but were not compared with LAAC [26, 46] (see Table 2).

3.4.2 Rate Control Strategies in High-Income Countries

Only one study was identified to evaluate interventions for rate control [10]. Propranolol was the optimal strategy to control abnormal heart rate due to AF when compared with betaxolol, bevantolol, bisoprolol, diltiazem and verapamil.

3.4.3 Rhythm Control Strategies in High-Income Countries

In patients at low risk of stroke, catheter ablation was the optimal strategy to control heart rhythm in patients with paroxysmal AF when compared with anti-arrhythmic drugs (AADs) alone [56, 62]. Convergent procedure was a more efficient strategy in patients with persistent AF when compared with AAD and catheter ablation [57]. A comparison of AADs alone showed that sotalol was the optimal choice when compared with atenolol, pilsicainide, flecainide, propafenone, dronedarone and amiodarone [10]. Risk factor management (RFM) was cost effective in controlling heart rhythm when compared with no RFM [61].

In patients at moderate risk of stroke, catheter ablation was the optimal strategy to control heart rhythm in patients with paroxysmal or persistent AF when compared with AADs alone [59]. Convergent procedure was the optimal intervention in patients with persistent AF when compared with AADs and catheter ablation [57].

In patients at high risk of stroke, catheter ablation was the optimal strategy to control heart rhythm in patients with paroxysmal, persistent or permanent AF when compared with AADs alone [58, 60]. Convergent procedure was the optimal intervention in patients with persistent AF when compared with AADs and catheter ablation [57] (see Table 2).

3.4.4 Stroke Prevention Strategies in Middle-Income Countries

In patients at low to moderate risk of stroke, apixaban was the optimal choice in three studies [49, 50, 52], which compared it with warfarin, dabigatran, edoxaban and rivaroxaban. Rivaroxaban was the optimal choice in two studies [54, 55] which compared it with apixaban, dabigatran, warfarin and LMWH, while warfarin was the cost-effective strategy in a single study [51].

In patients at high risk of stroke, one study showed that high dose edoxaban (60mg) was the optimal choice [53] (see Table 3).

3.4.5 Rhythm Control Strategies in Middle-Income Countries

In patients at moderate or high risk of stroke with paroxysmal AF, a study which compared AAD with CA showed that CA was the optimal strategy [63]. A study which compared AADs with RFCA and cryoballoon catheter ablation [64], and another study which compared cryoballoon catheter ablation with RFCA [65], both showed that RFCA was the optimal strategy for rhythm control (see Table 3).

A summary of the evidence is provided in Table 4.

4 Discussion

This systematic review evaluated the contemporary available evidence around the optimal management of all subtypes of AF. Data were collected and synthesised from studies conducted over the last decade (2012–2022) in both high- and middle-income countries. Treatment strategies were identified for stroke prevention, rate control and rhythm control. All included studies evaluated non-valvular atrial fibrillation. From this review, apixaban is suggested as the optimal strategy in HIC for stroke prevention in patients with low or moderate risk of stroke, while dabigatran is suggested as a next optimal strategy. In patients at high risk of stroke, LAAC is suggested as an optimal strategy, except where an occlusion procedure is contraindicated in the patients, while PG-guided warfarin is considered as second-line therapy. There is limited evidence to inform the decision to apply rate control. However, based on the available evidence, propranolol was the optimal choice in patients without bronchial asthma, peripheral vascular disease, diabetes mellitus or any other contraindications. In respect to rhythm control, for patients at low to moderate risk of stroke in HIC, catheter ablation is suggested for paroxysmal or persistent AF, while convergent procedure is reserved for persistent to permanent AF. Where catheter ablation or hybrid procedure is contraindicated and AAD is recommended, sotalol is the suggested option. In MICs, there are limited evidence to inform decision making. Available evidence lends priority to the use of apixaban for stroke prevention in patients at low and moderate risk of stroke, followed by rivaroxaban. Where there is substantial financial constraint, warfarin is suggested as the optimal choice. High dose edoxaban is suggested for patients at high risk of stroke, but this recommendation needs to be

Table 2 Cost effectiveness of management strategies in high-income countries

Author, year and reference	Price year, and currency	Study perspective	Class of atrial fibrillation	Base-case intervention	Comparator(s)	Willingness-to-pay threshold	ICER (as reported in original studies)	ICER in 2021 US dollars	Cost-effective strategy
Stroke prevention for low risk of stroke patients									
Kongnakorn et al., 2015 [30]	2013, Euro	Payer	All classes	Warfarin	Apixaban; dabigatran; rivaroxaban	€30,000	Apixaban 5mg: €7212/QALY	Apixaban 5 mg: 9960/QALY	Apixaban
Lee et al., 2016 [33]	2014, USD	Provider	All classes	Warfarin	Aspirin; clopidogrel + aspirin; LAAC; dabigatran; apixaban; rivaroxaban	$50,000	LAAC: $6298/QALY	LAAC: 7112/QALY	LAAC
Rognoni et al., 2014 [37]	2013, Euro	Payer	All classes	Warfarin	Apixaban; dabigatran; rivaroxaban	€25,000	Apixaban 5 mg: €9631/QALY	Apixaban 5 mg: 14,574/QALY	Apixaban
Verhoef et al., 2014 [40]	2012, Euro	Provider	All classes	Coumarin derivative	Apixaban; dabigatran; rivaroxaban	€20,000	**The Netherlands**, Apixaban: €13,024/QALY. **UK**, Dabigatran: €11,172/QALY.	**The Netherlands**. Apixaban: 18,422/QALY. **UK**. Dabigatran: 15,803/QALY	Apixaban and Dabigatran
Verhoef et al., 2016 [41]	2014, GBP, SEK	Provider	All classes	Std of care	Pharmacogenetic-guided warfarin	£20,000 (UK); 500,000 SEK (Sweden)	**UK**, £6702/QALY. **Sweden**, 253,848 SEK	**UK**, 10,885/QALY. **Sweden**, 33,040/QALY	Pharmacogenetic-guided warfarin
Wang et al., 2014 [43]	2012, USD	Provider	Paroxysmal	Warfarin	Dabigatran; rivaroxaban	$58,500	Rivaroxaban: $26,727/QALY	Rivaroxaban: 31,291/QALY	Rivaroxaban
Stroke prevention for moderate risk of stroke patients									
Athanasakis et al., 2015 [18]	2013, Euro	Payer	All classes	Apixaban	Dabigatran; rivaroxaban	€30,000	Apixaban: ≤ €13,727/QALY (relative to comparators)	Apixaban: ≤ 24,302/QALY (relative to comparators)	Apixaban
Canestaro et al., 2013 [19]	2011, USD	Societal	All classes	Warfarin	Apixaban; dabigatran; rivaroxaban	$100,000	Apixaban: $93,063/QALY	Apixaban: 111,043/QALY	Apixaban
Cervantes et al., 2022 [20]	2018, Euro	Payer	All classes	Warfarin	Apixaban; dabigatran; rivaroxaban	€22,000	Rivaroxaban: €952/QALY.	Rivaroxaban: 1560/QALY.	Rivaroxaban
Choi et al., 2022 [21]	2020, USD	Provider	All classes	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	$32,000	Apixaban: $8427/QALY.	Apixaban: 8602/QALY	Apixaban

Table 2 (continued)

Author, year and reference	Price year, and currency	Study perspective	Class of atrial fibrillation	Base-case intervention	Comparator(s)	Willingness-to-pay threshold	ICER (as reported in original studies)	ICER in 2021 US dollars	Cost-effective strategy
Coyle et al., 2013 [22]	2011, CAD	Payer	All classes	Warfarin	Apixaban; dabigatran; rivaroxaban	$50,000	Dabigatran 150 mg: $20,797/QALY; Apixaban: $24,312/QALY	Dabigatran 150 mg: 19,975/QALY; Apixaban: 23,351/QALY	Dabigatran 150 mg was optimal if the $CHADS_2$ score was less than 2 or more than 2 with previous minor stroke
de Jong et al., 2019 [23]	2018, Euro	Societal	All classes	Apixaban	Warfarin; dabigatran; edoxaban; rivaroxaban	€20,000	Apixaban: €3506/QALY	Apixaban: 4665/QALY	Apixaban
Freeman et al., 2016 [24]	2014, USD	Payer	All classes	LAAC	Dabigatran; warfarin	$50,000	LAAC versus warfarin: $20,486/QALY. dabigatran: $23,422/QALY	LAAC versus warfarin: 23,133/QALY. dabigatran: 26,448/QALY	LAAC
Harrington et al., 2013 [25]	2012, USD	Provider	All classes	Warfarin	Apixaban; dabigatran; rivaroxaban	$50,000	Apixaban 5 mg: $15,026/QALY.	Apixaban 5 mg: 17,592/QALY.	Apixaban
Janzic and Kos, 2015 [27]	2014, Euro	Payer	All classes	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	€25,000	Genotype-guided warfarin dosing: $6959/QALY.	Genotype-guided warfarin dosing: 12,896/QALY	Pharmacogenetic-guided warfarin
Micieli et al., 2016 [34]	2012, CAD	Payer	Paroxysmal	LAAC	Apixaban; dabigatran; warfarin; rivaroxaban	$50,000	Apixaban: $28,167/QALY	Apixaban: 20,782/QALY	Apixaban
Pradelli et al., 2014 [35]	2013, Euro	Payer	All classes	Apixaban	Dabigatran; rivaroxaban	€20,000	Apixaban: €3882/QALY.	Apixaban: 5874/QALY.	Apixaban
Rognoni et al., 2014 [37]	2013, Euro		All classes	Warfarin	Apixaban; dabigatran; rivaroxaban	€25,000	Dabigatran: €7609/QALY	Dabigatran: 11,514/QALY	Dabigatran
Shah et al., 2016 [8]	2015, USD	Payer	All classes	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	$100,000	Apixaban: $25,816/QALY	Apixaban: 28,843/QALY	Apixaban
Vargas et al., 2018 [39]	2015, USD	Payer	All classes	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	$100,000	Edoxaban: $86,882/QALY	Edoxaban: 97,068/QALY	Edoxaban

Table 2 (continued)

Author, year and reference	Price year, and currency	Study perspective	Class of atrial fibrillation	Base-case intervention	Comparator(s)	Willingness-to-pay threshold	ICER (as reported in original studies)	ICER in 2021 US dollars	Cost-effective strategy
Walter et al., 2021 [42]	2018, Euro	Provider	All classes	Apixaban	Warfarin; dabigatran; edoxaban; rivaroxaban	€28,000	Apixaban: €12,743/QALY	Apixaban: 16,156/QALY	Apixaban
Wong et al., 2020 [44]	2018, CAD	Payer	All classes	Aspirin	Apixaban; dabigatran; edoxaban; rivaroxaban; warfarin	$50,000	Apixaban: $5517/QALY	Apixaban: 4848/QALY	Apixaban
Zhao et al., 2016 [47]	2015, USD	Payer	All classes	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	$49,700	Apixaban: $24,476/QALY	Apixaban: 27,348/QALY	Apixaban
Zheng et al., 2014 [48]	2013, GBP	Payer	All classes	Dabigatran	Apixaban; warfarin; rivaroxaban	£25,000	Dabigatran: dominates	Dabigatran: dominates	Dabigatran
Stroke prevention for patients at high risk of stroke									
Hospodar et al., 2018 [26]	2015, USD	Payer	All classes	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	$100,000	Warfarin: dominates	Warfarin: dominates	Warfarin (for patients who can achieve TTR of 70%)
Labori et al., 2022 [31]	2020, Euro	Provider; societal	All classes	Std of care	LAAC	€45,829	LAAC: €4047/QALY (provider). Cost-saving (societal)	LAAC: 466/QALY (provider). Cost-saving (societal)	LAAC
Lanitis et al., 2014 [32]	2012, Euro	Payer	All classes	Warfarin	Apixaban; Aspirin; dabigatran; edoxaban; rivaroxaban	€30,000	Apixaban: €12,227/QALY	Apixaban: 17,077/QALY	Apixaban
Reddy et al., 2018 [36]	2016, USD	Payer	All classes	LAAC	Warfarin; apixaban; dabigatran	$50,000	LAAC: dominates	LAAC: dominates	LAAC
Rognoni et al., 2014 [37]	2013, Euro	Payer	All classes	Warfarin	Apixaban; dabigatran; rivaroxaban	€25,000	Apixaban: €4723/QALY	Apixaban: 7147/QALY	Apixaban
Saw et al., 2016 [38]	2015, CAD	Payer	All classes	Aspirin (patients contraindicated for OACs)	LAAC	Not defined	LAAC: dominates	LAAC: dominates	LAAC

Table 2 (continued)

Author, year and reference	Price year, and currency	Study perspective	Class of atrial fibrillation	Base-case intervention	Comparator(s)	Willingness-to-pay threshold	ICER (as reported in original studies)	ICER in 2021 US dollars	Cost-effective strategy
Wu et al., 2021 [45]	2018, USD	Payer	All classes	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	$50,000	Edoxaban: $15,864/QALY;	Edoxaban: 16,826/QALY	Edoxaban
You Joyce, 2015 [46]	2015, USD	Payer	Paroxysmal	Genotype-guided DOAC	Universal use of DAOC	$50,000	DOAC: $314,129/QALY	DOAC: 350,959/QALY	Pharmacogenomic-guided warfarin
Shah et al., 2016 [8]	2015, USD	Payer	All classes	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	$100,000	Dabigatran: $31,435/QALY	Dabigatran: 35,120/QALY	Dabigatran
Rate control for patients at low risk of stroke									
Kim et al., 2019 [10]	2017, USD	Societal	All classes	Atenolol	Propranolol; betaxolol; bevantolol; bisoprolol; diltiazem; verapamil	$30,000	Propranolol: cost saving	Propranolol: cost saving	Propranolol
Rhythm control for patients at low risk of stroke									
Khaykin et al., 2015 [56]	2012, USD	Payer	Paroxysmal	AAD	CA	$50,000	Ablation: Lifetime: $1228/QALY. 10 year: $22,879/QALY.	Ablation: Lifetime: 1 438/QALY. 10 year: 26,786/QALY.	CA (for a lifetime or minimum of 10 years)
Anderson et al., 2014 [57]	2013, USD	Payer	Persistent	AAD	Convergent procedure; CA	Not defined	CA: $30,596/QALY; Convergent: $20,640/QALY	CA: 35,202/QALY; Convergent: 23,748/QALY	Convergent procedure
Kim et al., 2019 [10]	2017, USD	Societal	All classes	Atenolol	Sotalol; Pilsicainide Flecainide; Propafenone Dronedarone; Amiodarone	$30,000	Sotalol: $227/QALY.	Sotalol: 246/QALY.	Sotalol
Pathak et al., 2017 [61]	2010, AUD	Provider	Paroxysmal and persistent	No RFM	RFM	Not defined	RFM: −$52,305/QALY (4 year). −$62,653/QALY (10 year)	RFM: Cost saving (4 year). Cost saving (10 year)	Risk factor management
Reynolds et al., 2014 [62]	2011, GBP	Payer	Paroxysmal	AAD	Cryoballoon ablation	£30,000/QALY	Cryoballoon: £21,957/QALY	Cryoballoon: 37,525/QALY	Cryoballoon ablation

Table 2 (continued)

Author, year and reference	Price year, and currency	Study perspective	Class of atrial fibrillation	Base-case intervention	Comparator(s)	Willingness-to-pay threshold	ICER (as reported in original studies)	ICER in 2021 US dollars	Cost-effective strategy
Rhythm control for patients at moderate risk of stroke									
Anderson et al., 2014 [57]	2013, USD	Payer	Persistent	AAD	Convergent procedure; CA	Not defined	CA: $11,175/QALY. Convergent: $2214/QALY	CA: 12,857/QALY. Convergent: 2547/QALY	Convergent procedure
Lau et al., 2021 [59]	2018, CAD	Payer	Paroxysmal and persistent	AAD	CA	$50,000	CA: $35,360/QALY	CA: 31,071/QALY	CA
Rhythm control for patients at high risk of stroke									
Anderson et al., 2014 [57]	2013, USD	Payer	Persistent	AAD	Convergent procedure; CA	Not defined	Convergent versus CA: dominant	Convergent: dominant	Convergent procedure
Chew et al., 2022 [58]	2018, USD	Provider	Persistent	AAD	Catheter ablation	$100,000	Catheter ablation: $57,893/QALY	Catheter ablation: 61,403/QALY	Catheter ablation
Leung et al., 2022 [60]	2019, GBP	Payer	All classes	AAD	Catheter ablation	£20,000	£8614/QALY	12,869/QALY	Catheter ablation
Mixed treatment strategy: rhythm control and stroke prevention									
Kimura et al., 2017 [29]	2014, Yen	Payer	Paroxysmal AF	CA + warfarin	CA + dabigatran	¥6,000,000	CA + warfarin: ¥3.45–5.70 M/QALY. CA + dabigatran: ¥3.81M–8.08M/QALY	CA + warfarin: 62,896/QALY. CA + dabigatran: 89,158/QALY	CA + warfarin for low to moderate risk of stroke. CA + dabigatran for high risk of stroke
Kawakami et al., 2021 [28]	2020, USD	Provider	All classes	CA + std OAC	CA + LAAC	$50,000/QALY	CA + LAAC strategy: $11,072/QALY	CA + LAAC strategy: 11,302/QALY	CA + LAAC

AAD anti-arrhythmic drugs, *AF* atrial fibrillation, *CA* catheter ablation, *LAAC* left atrial appendage closure, *OAC* oral anti-coagulant, *QALY* quality-adjusted life-years, *RFCA* radiofrequency catheter ablation, *RFM* risk factor management, *TTR* time to therapeutic range, *USD* United States dollars, *VKA* vitamin K antagonist

Table 3 Cost effectiveness of management strategies in middle-income countries

Author, year and reference	Price year, and currency	Study perspective	Class of atrial fibrillation	Base-case intervention	Comparator	Willingness-to-pay threshold	ICER (as reported in original studies)	ICER in 2021 US dollars	Cost-effective strategy
Stroke prevention for patients at low to moderate risk of stroke									
Dilokthornsakul et al., 2020 [51]	2017, Thai Baht	Societal	All classes	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	160,000 THB	All comparators: > 160,000 THB/QALY	All comparators: > 13,926/QALY	Warfarin
Liao et al., 2020 [49]	2016, USD	Payer	All classes	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	$20,000	Apixaban 5 mg: $4115/QALY	Apixaban 5 mg: 4548/QALY	Apixaban
Liu and Chen, 2017 [50]	2012, USD	Payer	All classes	Apixaban	Dabigatran; warfarin; rivaroxaban	$50,000	Apixaban: ≤ $48,896/QALY compared with each comparator	Apixaban: ≤ 57,245/QALY	Apixaban
Mendoza et al., 2019 [52]	2015, USD	Payer	All classes	Apixaban	Dabigatran; warfarin; rivaroxaban	$9000/QALY	Apixaban: cost saving	Apixaban: cost saving	Apixaban
Sun et al., 2021 [54]	2021, USD	Payer	All classes	LMWH + VKA	Apixaban; dabigatran; rivaroxaban	$32,921	Rivaroxaban: dominates	Rivaroxaban: dominates	Rivaroxaban
Zhou et al., 2022 [55]	2020, USD	Provider	All classes	Warfarin	Apixaban; dabigatran; rivaroxaban	$31,544	Rivaroxaban: $−1123/QALY (Ab. dominant)	Rivaroxaban: −1146/QALY (Ab. dominant)	Rivaroxaban
Stroke prevention for patients at high risk of stroke									
Rattanachotphanitet al., 2019 [53]	2017, USD	Societal; payer	All classes	Warfarin	Apixaban; dabigatran; edoxaban; rivaroxaban	$5,842	Edoxaban 60 mg: $9704/QALY	Edoxaban 60 mg: 10,524/QALY	Edoxaban
Rhythm control for patients at moderate risk of stroke									
Hu et al., 2022 [64]	2020, USD	Provider	Paroxysmal	AAD	STAI (RFCA); second generation cryoballoon ablation (CB2)	$30,390	STAI: $5927/QALY; CB2: $12,167/QALY	STAI: 6050/QALY; CB2: 12,420/QALY	STAI (RFCA)
Du et al., 2019 [63]	2014, Yuan	Payer	Paroxysmal and persistent	AAD	CA	¥139,956	CA: ¥66,764/QALY	CA: 21,301/QALY	CA
Rhythm control for patients at high risk of stroke									
Sun et al., 2019 [65]	2016, USD	Payer	Paroxysmal	Cryoballoon ablation	RFCA	$25,306	RFCA: $−35,060/QALY (cost saving)	RFCA: −38,747/QALY (cost saving)	RFCA

AAD Anti-arrhythmic drugs, *CB2* second generation cryoballoon catheter ablation, *LMWH* low molecular weight heparin, *QALY* quality-adjusted life-years, RFCA radiofrequency catheter ablation, *STAI* Thermo-Cool Smart-Touch guided by ablation index, *THB* Thai baht, *USD* United States dollars, *VKA* vitamin K antagonist

strengthened with additional evidence. In rhythm control in MICs, radiofrequency catheter ablation is suggested in patients at moderate to high risk of stroke.

This systematic review is the first to holistically evaluate stroke prevention, cardiac rate and cardiac rhythm control strategies in AF management while considering the difference in economic development (whether low-, middle- or high-income country) where management is being applied. We ensured that included studies on stroke prevention evaluated the relative efficiency of two or more DOACs in head-to-head comparisons. The included studies were also recently (within the last decade) conducted economic evaluations.

Previously conducted systematic reviews have shown that for stroke prevention, the DOACs are cost effective, but it is unclear which of the DOAC is most cost effective [66–68]. Although, some systematic reviews have indicated that apixaban was the optimal strategy when compared with other DOACs [69, 70]. The findings are similar to the European guideline on AF management which recommends the use of DOACs in patients with one major risk factor or ≥ 2 clinically relevant non-major risk factors; the use DOAC or aspirin in patients with one clinically relevant non-major risk factor with preference for DOAC; and the use of aspirin in patients without risk factors [1]. In rate control, the guideline recommend the use of beta blockers, calcium-channel blockers, digitalis or a combination; also recommending that the choice of medication should be individualized and the dose monitored to avoid bradycardia [1]. The guideline also recommends that catheter ablation be reserved in patients with AF who remain symptomatic despite optimal medical therapy [1]. In MICs, a meta-analysis showed that DOACs were not cost effective compared with VKA [71], but in HICs, DOACs were cost effective. In cardiac rhythm control, a systematic review showed that catheter ablation was not cost effective as a first line compared with AAD as there was insufficient evidence to support the superiority of catheter ablation over AAD [72]. Our systematic review provides additional evidence to the cost effectiveness of DOACs in stroke prevention, with the likelihood of apixaban being the most optimal intervention. Our systematic review also provided supporting evidence that VKA is still potentially cost effective in MICs. However, it provided new evidence that catheter ablation can be cost effective and considered as first line compared with AAD, as opposed to a previous systematic review [72].

The studies included in this review have some important limitations. Most used data from the same clinical trials, which may not be ideal for the population for which the economic evaluation was performed. The trials itself lack head-to-head comparison of interventions. A comparison of one intervention to the standard of care may not provide the optimal treatment strategy because other interventions were not compared. A comparison of multiple treatment strategies is more reliable as it provides evidence on the relative efficiency between the different strategies. Generally, population-specific data were lacking in most studies included in the review. There were very limited studies in the literature that evaluated rate and rhythm control treatment strategies. All these limitations underscore the need for more population-specific clinical trials, head-to-head trials and other relevant population-specific studies to provide more robust data for economic evaluation. The value of information analysis may be pertinent in understanding the value that trials may offer and potentially help to inform their design.

This systematic review, likewise, has some limitations. Based on the available evidence, the recommendations provided here are only suggestive and do not necessarily apply to all settings. Due to limited head-to-head trials, the results from this systematic review indicate the need for more RCTs or potentially real-world evidence approaches on the interventions indicated for AF management to provide stronger evidence, which will in turn be used to conduct new economic evaluations to support decision making. Thus, the results of this review should be interpreted with caution, and treatment should always be individualised and guided by sound clinical evidence. Also, with the varying structure and funding of health systems across the world, heterogeneity in the studies' characteristics and the limited evidence, a quantitative synthesis of evidence was not considered. The limited number of available studies, especially for cardiac rate and rhythm control, makes it difficult for generalisability of findings. More economic evaluations on rate and rhythm control strategies would provide stronger evidence. Hence, future economic evaluations especially on rate control strategies are necessary. The thresholds for risk of bias classification of the CHEC checklist developed by the authors may not be the best approach and may have some limitations. Hence, caution is needed when using our developed check list as well as the interpretation of our findings. The grouping of studies by income-level classification is not ideal to adequately control for heterogeneity. While grouping by income-level classification may control for heterogeneity in the cost component of the ICER, it does not control for potential heterogeneity in the effectiveness of the interventions which is dependent on several covariates including race, pharmacogenetics, comorbidities, lifestyle, environment, etc. Future studies should also consider a regression analysis to test for the effect of these covariates on the ICER, which may inform the need for subgroup analysis in the future.

Table 4 Summary of evidence for the optimal strategies

Treatment strategy	Low risk of stroke	Moderate risk of stroke	High risk of stroke
High-income countries			
Stroke prevention	Apixaban	Apixaban Dabigatran	LAAC PG-guided warfarin
Rate control	Propranolol	Propranolol	Propranolol
Rhythm control	Catheter ablation in paroxysmal AF Convergent procedure in persistent AF Sotalol in patients with compelling need for AADs	Catheter ablation in paroxysmal or persistent AF Convergent procedure in persistent AF	Catheter ablation in paroxysmal, persistent, or permanent AF Convergent procedure in persistent AF
Middle-income countries			
Stroke prevention	Apixaban Rivaroxaban Warfarin in cases of financial constraint	Apixaban Rivaroxaban Warfarin in cases of financial constraint	High dose of Edoxaban
Rhythm control		Radiofrequency catheter ablation	Radiofrequency catheter ablation

AF atrial fibrillation, *LAAC* left atrial appendage closure, *PG-Warfarin* Pharmacogenetic-guided warfarin

5 Conclusions

Based on the available evidence, in high-income countries, the review suggests the use of apixaban in patients at low and moderate risk of stroke, and LAAC in patients at high risk. Propranolol should be considered for rate control in patients without contraindication due to cardioselectivity. Catheter ablation and convergent procedure are suggested in paroxysmal and persistent AF, respectively. In middle-income countries, apixaban is suggested for stroke prevention while warfarin should be considered in the case of financial constraint. Radiofrequency catheter ablation is suggested in rhythm control.

Due to limited clinical trials on AF management strategies, the lack of head-to-head trials (especially on the new oral anti-coagulants), the heterogeneity in clinical characteristic of the trials from which the data used in most of the included studies in this review were derived from, and the variations in the modelling methods amongst the studies, the decision to use any treatment strategy should always be individualised and guided by strong objective and subjective clinical and economic evidence in a multi-disciplinary team setting.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40273-023-01276-5.

Declarations

Ethical approval and consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials Data used in the study are provided in the supplementary file.

Competing interest Charles Okafor, Joshua Byrnes, Simon Stewart, Paul Scuffham and Clifford Afoakwah have no conflict of interest to declare.

Funding Open Access funding enabled and organized by CAUL and its Member Institutions. CA received funding support from the Griffith University Health Group Seed Grant. SS is supported by the NHMRC of Australia (GNT1135894) and PS was the recipient of a NHMRC Fellowship (GNT1136923).

Authors' contributions CO, CA and JB developed the study design. CO and CA were responsible for data collection and extraction. CO undertook the data analyses and led the preparation of the initial draft. All authors (CO, JB, SS, PS and CA) contributed to the interpretation of results and drafting the manuscript. All authors reviewed the final manuscript.

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Authors and Affiliations

Charles Okafor[1,2] · Joshua Byrnes[1,2] · Simon Stewart[2,3] · Paul Scuffham[1,2] · Clifford Afoakwah[1,2]

✉ Clifford Afoakwah
c.afoakwah@griffith.edu.au

[1] Centre for Applied Health Economics, School of Medicine and Dentistry, Griffith University, 170 Kessels Road, Nathan, QLD 4111, Australia

[2] Menzies Health Institute Queensland, Griffith University, Southport, QLD, Australia

[3] Institute for Health Research, University of Notre Dame Australia, Freemantle, WA, Australia