ISSN: 2689-4246
DOI: 10.33552/CTCMS.2021.02.000539
Current Trends in Clinical & Medical Sciences
Iris Publishers

Review Article

Pharmacoeconomic Evaluation of Novel Oral Anticoagulants in Patients with Cardiovascular Diseases: A Systematic Review

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Received Date: January 12, 2021

Published Date: February 04, 2021

Abstract

Background: Several economic evaluations have been performed in various countries to demonstrate the efficacy of novel oral anticoagulants versus warfarin in patients with cardiovascular diseases. This systematic review aims to provide a comprehensive summarization of the pharmacoeconomic performance of four novel oral anticoagulants, rivaroxaban, apixaban, edoxaban and dabigatran usage in patients with cardiovascular diseases.

Methods: Relevant databases including Embase, Cochrane Library, Medline, CINAHL and Science Direct were used to search for qualitative and quantitative studies. The reviewers independently extracted data according to PRISMA checklist.

Results: There were 43 studies found according to the inclusion criteria. We identified six types of intervention including cost-effectiveness comparison between the novel oral anticoagulants, cost-effectiveness comparison between the novel oral anticoagulants and warfarin, apixaban to warfarin, dabigatran to warfarin, rivaroxaban to warfarin, and edoxaban to warfarin. Outcomes of the interventions included Quality-adjusted Life Year (QALY) , Incremental Cost-effectiveness Ratio (ICER), Incremental Cost-utility Ratio (ICUR), Life Year Gained (LYG), mean-life years, life expectancy, the rate of recurrence, Confidence Interval (CI), willingness-to-pay, number of strokes prevented and types of costs.

Conclusion: Numerous studies investigated novel oral anticoagulants since they were introduced to clinical practice, especially for their various roles in management of cardiovascular diseases. With proven NOAC clinical superiority and the lower need of follow-up visits and lab tests, NOAC economic profile is a broad area of research. The current study managed to review 43 studies investigating NOACs. Despite the variations in quality, sampling, design of studies investigating NOACs, all studies reported that NOAC are more cost-effective than warfarin in terms of indirect costs and quality-adjusted life year.

Keywords: Pharmacoeconomic; Cost-effectiveness; Novel oral anticoagulants; Dabigatran; rivaroxaban; Apixaban; Edoxaban; Cardiovascular diseases

Introduction

For decades, the oral anticoagulant warfarin remained the gold standard of medical management for many cardiovascular diseases and main pharmacological agents for the prophylaxis of venous thromboembolism [1]. Among these cardiovascular patients, the vitamin K antagonists are especially beneficial to patients with venous thromboembolism and for the prevention of stroke. In terms of clinical consideration, warfarin displays several limitations and disadvantages. The narrow therapeutic window and vast drug-drug and drug-food interactions properties of warfarin render it clinically difficult to use [2]. Precise dose adjustment and frequent dose monitoring are of utmost importance because inappropriate dose can lead to many adverse clinical events. Warfarin over-dose

will increase the risk of serious bleeding while under-dose will not produce the therapeutic outcomes desired, for example stroke prevention [3].

Novel oral anticoagulants (NOACs) are becoming more important in clinical uses due to the limitations of warfarin mentioned above. NOACs can be divided into direct factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) and direct thrombin inhibitors (dabigatran). In terms of bleeding risk, NOACs display a significantly lower risk of intracranial and intracerebral bleeding than warfarin [4]. NOACs display evidence that they are at least as effective as warfarin if not superior to warfarin in the clinical treatment of patients with systemic embolism and as a prophylaxis for stroke in atrial fibrillation patients [5-6].

Even though NOACs show a superior performance in clinical uses compared to warfarin, but the main drawback on prescribing NOACs to patients instead of warfarin is due to the high daily costs. The rising clinical importance of NOACs, as well as their higher cost, impose a question on the pharmacoeconomic performance of the NOACs. There are numerous studies done in many countries to evaluate the pharmacoeconomic profile of the NOACs.

The aim of this systematic review is to evaluate the pharmacoeconomic performance of four novel oral anticoagulants, rivaroxaban, apixaban, edoxaban and dabigatran usage in patients with cardiovascular diseases (deep vein thrombosis, pulmonary embolism, atrial fibrillation and stroke).

Methodology

A search was conducted in Google Scholar, Embase, Cochrane Library, Medline, CINAHL and Science Direct using search algorithms to identify relevant pharmacoeconomic publications of novel oral anticoagulants in patients with cardiovascular diseases. Processes throughout systematic review were carried out using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. The search identified publications with the keywords pharmacoeconomic, cost-effectiveness, novel oral anticoagulants, dabigatran, rivaroxaban, apixaban, edoxaban, cardiovascular diseases, stroke, atrial fibrillation, deep vein thrombosis or pulmonary embolism. Both cost studies and economic evaluation of novel oral anticoagulants were considered.

While cost studies estimate expenses associated with a particular treatment for cardiovascular diseases, economic evaluations assess both health costs and benefits associated with a drug against its comparator(s). Economic evaluations usually include cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses depending on how health benefits [natural units, quality-adjusted-life-years (QALYs)] and monetary terms are measured. QALYs incorporated both morbidity (as the quality of life) and mortality. Cost-effectiveness analyses looks at a single quantified effectiveness measure of the cost per unit. There are many variations in cost-effectiveness analyses that can be considered; cost consequence and cost-minimization analyses, with comparing cost outcomes due to health benefits. Economic evaluation in health care consider the resources consumed by patients, productivity losses, health sector and other sectors as well. A treatment is usually considered cost-effective if the incremental cost-effectiveness ratio (ICER) is below the commonly used threshold for the given country. Various threshold are available such as $50,000 per QALY in the United States and $20,000-$100,000 per QALY in Canada.

The title and/or abstract of articles published between 2008 and 2018 pertaining to novel oral anticoagulants were searched for the keywords. “Grey” literature (ie, material that can be referenced, but is not published in peer-reviewed, indexed medical journals) was not examined and not included in this review. From the review questions, the author concluded that the question is a therapy question. Hence, the best evidence would be a randomized controlled trial, cohort study, and case-control. Abstracts were included when all of the following were true: cost-effectiveness of different novel oral anticoagulants on patients with cardiovascular diseases and published from 2008 to 2018. Articles published in English language only were accepted; those that did not meet the pre-stated criteria were excluded. Different types of novel oral anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban) used in patients with cardiovascular diseases were included in this review. Articles that have not mentioned novel oral anticoagulants were excluded. Patients with cardiovascular diseases (stroke, deep vein thrombosis, pulmonary embolism and atrial fibrillation); any gender; any age and any severity of cardiovascular diseases were included in this review. Populations were not restricted to one country or place. All papers around the world will be examined and reviewed.

For data extraction, data extracted from included studies using data extraction from guided by standardized extraction data tool by Cochrane Collaboration. The extracted data assured to match with the review question and fulfill the review objectives. A table was used to present details of the characteristic of included studies, such as author, country, year of study; interventions, sample and study design. Data on study design, inputs, results and authors’ conclusions were extracted.

Results

Study Selection

At the beginning, 120 publications were retrieved from EMBASE, Google Scholar, Pubmed, Cochrane, CINAHL and Science Direct. From going through the references of the 120 publications, an additional six publications were identified owing up to the total of 126 publications chosen for further screening. The numbers were narrowed down to 95 after removing the duplicates. After the literature was screened for eligibility, 43 articles were included in

the qualitative synthesis and 52 publications were excluded due to the reasons stated in Figure 1. A vast majority of the articles were removed due to the fact that they were only systematic reviews. Other reasons for exclusion included reasons such as the articles not being associated with pharmacoeconomics or cost-effectiveness, the irrelevance of the literature to the Novel Anti Coagulants of interest, the publications were in the form of meta-analysis as well as the articles retrieved were not available in English.

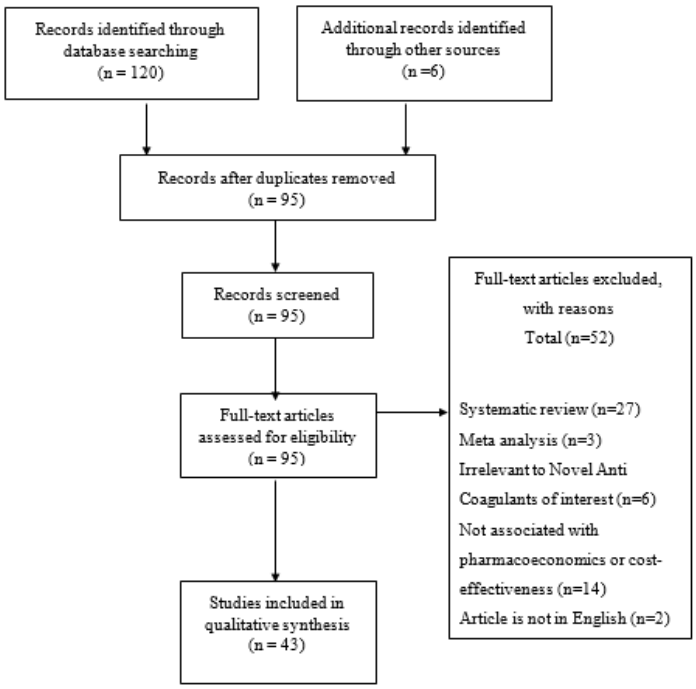

Figure 1: Flow diagram of publications included and excluded in the review.

Characteristics of Studies

Among the studies, the sample size was in the range of 100 to 50,000 patients from all over the world. This review included randomized controlled trials, cohort and case-control studies from the year of 2010 to 2017. Three studies were conducted in Germany, nine in the United Kingdom, one in Japan, Slovenia, Australia, Singapore, Sweden, California, Hong Kong, Ireland, France, Portuguese respectively, two in Sweden, four in the Netherlands, seven in the United States of America, two in Canada, two in England and five were unclear. 25 studies were using Markov model, five studies were using Randomized Control Trials (RCT) together with a cohort study, six using cohort study only and Randomized Control Trials (RCT) only besides one using retrospective observational study.

Across studies, the reported outcome of interest differed considerably. Reported objective measures of cost-effectiveness included Quality-adjusted Life Year (QALY), Incremental Cost-effectiveness Ratio (ICER), Incremental Cost-utility Ratio (ICUR), Life Year Gained (LYG), mean-life years, life expectancy, rate of recurrence, Confidence Interval (CI), willingness-to-pay, number of strokes prevented and types of costs such as direct medical cost, long-term care cost, costs accumulated, total medical costs, medical cost avoidance and clinical event costs avoided.

Cost-effectiveness comparison among the novel oral anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban)

This review identified 7 primary studies examining the comparison of the cost-effectiveness of new oral anticoagulants. Most studies were retrospective analyses reporting quality-adjusted life years (QALY), total costs, and incremental cost-effectiveness ratios (ICER). 4 of the studies were conducted in the United Kingdom with 1 from the Netherlands and the last two were unknown setting.

In the UK (2015), patients received dabigatran (7.68 QALYs) has higher QALYs compare to apixaban (7.63 QALYs) and rivaroxaban (7.47 QALYs). For the lifetime cost, dabigatran also is the cheapest when compared to other novel oral anticoagulants. The total lifetime costs are dabigatran ((£23,342), apixaban (£24,014) and rivaroxaban (£25,220) [7].

In 2014, ICER is £9611, £4497 and £5305 per QALY gained with apixaban compared with dabigatran 150 mg BID, dabigatran 110 mg BID, and rivaroxaban 20 mg once daily, respectively [8]. In terms of therapeutic management costs, compared with dabigatran 110mg, dabigatran 150mg, and rivaroxaban, respectively, apixaban yielded additional anticoagulant (drug) and management costs. The average cost-offsets in monitoring and clinical event–related costs (lifetime reduction) are £249, £140, and £269 [9].

The estimated incremental cost-effectiveness ratio was £9611, £4497, and £5305 per quality-adjusted life year gained with apixaban compared with dabigatran 150 mg BID, dabigatran 110 mg BID, and rivaroxaban 20 mg once daily, respectively [10]. Besides that, the annual total medical cost avoidances (2014) is dabigatran ($2,794), rivaroxaban ($2,948), apixaban 2.5 mg ($4,249) and apixaban 5 mg ($4,244) [11].

In the Netherlands (2014), QALYs were increased by rivaroxaban in 0.166, apixaban in 0.365 and dabigatran in 0.374. When ICER compared with the coumarin derivative, rivaroxaban showed - €34,248 per QALY gained, apixaban showed €13,024 per QALY gained and dabigatran showed €14,626 per QALY gained A willingness-to-pay threshold of €20,000 or €36,000 per QALY gained of apixaban is (37 and 42 %, respectively), dabigatran (41 and 48 %, respectively) and rivaroxaban (5 and 4 %, respectively) [12]. In conclusion, dabigatran yields more total QALYs at lower lifetime costs than apixaban and rivaroxaban.

Cost-effectiveness comparison among the novel oral anticoagulants to warfarin

Eight primary studies had identified as the comparison of the cost-effectiveness of new oral anticoagulants to warfarin or aspirin. Most studies were retrospective analyses reporting quality-adjusted life years (QALY), total costs, and incremental cost-effectiveness ratios (ICER) and willingness to Pay. 2 of the studies were conducted in United States 2 of them conducted in Canada with every 1 study from the German, Slovenia, Singapore and France respectively.

In the United State (2013), the total cost of warfarin is ($77 813), rivaroxaban 20 mg ($78 738±$1852), dabigatran 150 mg ($82 719±$1959), and apixaban 5 mg ($85 326±$1512). For the QALY, apixaban 5 mg is 8.47, dabigatran 150 mg is (8.41±0.07), rivaroxaban 20 mg is (8.26±0.06), and warfarin is (7.97±0.04). Cost-effectiveness of apixaban 5 mg is 45.1%, dabigatran 150 mg is 40%, whereby rivaroxaban 20 mg is 14.9%, and warfarin is 0%. The ICER is $15 026 per QALY gained [13]. Another study gave results that QALY is 9.38 for apixaban and 9.02 for warfarin. Total cost of warfarin was $46241and $58889 for rivaroxaban. In 2016, for ICER, apixaban showed $25816/QALY [14]. In the Canada (2013), one study showed QALYs for dabigatran is 6.543, rivaroxaban is 6.541 and 6.617 for dabigatran and apixaban. The total costs take $22804 for (dabigatran), $22016 for rivaroxaban, $21966 for apixaban, whereby $21486 for dabigatran and $18620 for warfarin. Another study provided an additional 0.506 life-years and 0.638 QALYs relative to warfarin [15]. A study from the German (2014) 7.56-7.64 QALYs was gained for warfarin whereby NOACs added additional 0.04-0.19 QALYs. The total cost of warfarin ranged from £7622 to 9069 and NOACs ranged from £19537 to 20048 [16].

In the Slovenia (2014), QALY for standard warfarin treatment with a mean TTR of 60.0 % is 7.218 QALYs. The highest average survival was estimated with apixaban, followed by dabigatran and edoxaban. These three medicines performed better than warfarin for more than 0.2 QALY (Janzic and Kos, 2015). In the Singapore (2014), QALYs for anticoagulants drug are warfarin (8.75), dabigatran 110 mg (8.73), dabigatran 150 mg (8.82), and rivaroxaban (9.33). The total costs of warfarin (SG$ 34,648), dabigatran 110mg (SG$54,919), dabigatran150mg (SG$50,484), and rivaroxaban (SG$51,975). The ICER of rivaroxaban versus warfarin is SG$29,697, approximate US$26,727 per QALY [18].

Lastly, in France (2014), the study concluded that warfarin and apixaban were the two optimal treatment choices, as the other five treatment strategies which including aspirin, dabigatran 110 mg, dabigatran in sequential dosages, dabigatran 150 mg, and rivaroxaban [19]. In a nutshell, in term of cost, QALYs, novel oral anticoagulants show higher cost-effectiveness than warfarin.

Cost-effectiveness comparison among the apixaban to warfarin

This review identified eight primary studies examining the comparison of the cost-effectiveness of apixaban to warfarin. These studies were retrospective analyses reporting quality-adjusted life years (QALY), total costs, and incremental cost-effectiveness ratios (ICER). Two of the studies were conducted in the United Kingdom and the United States respectively. One study is from the Japan, One from the Sweden and the one from the Australia. The last study, unfortunately the setting was unknown.

In the United Kingdom (2016), studies showed that apixaban was cost-effective compared with vitamin K antagonist at an incremental cost-effectiveness ratio of 2520 pounds per QALY gained and was a dominant alternative to either rivaroxaban or LMWH/Dabigatran [20]. On the other hand, in 2014, apixaban was projected to increase life expectancy and quality-adjusted life years (QALYs) compared with warfarin and aspirin. The estimated incremental cost-effectiveness ratio was £11909 and £7196 per QALY gained with apixaban compared with warfarin and aspirin, respectively [21].

In United State (2012), QALYS was 10.69 and 11.16 years for warfarin and apixaban respectively. The study showed total costs were $94,941 for warfarin and $86,007 for apixaban [22].

In another paper, the researcher concluded that apixaban is more cost-effective, although warfarin is superior if apixaban was 2% less effective than expected [23].

While in the Japan (2015), it showed that apixaban increases life expectancy by 0.231 year or 0.240 QALYs while treatment cost increased by ¥511,692 compared to warfarin. The incremental cost-effectiveness ratio was ¥2,135,743 per QALY. When the willingness-to-pay threshold was set at approximately ≥¥2,250,000 per QALY, the probability of apixaban being cost-effective was ≥50% [24]. A study in the Sweden (2014) concluded that in warfarin suitable population, the QALYs was 6,71 for apixaban and 6,51 for warfarin. For warfarin unsuitable population, the QALYs was 6.70 for apixaban and 6.41 for warfarin. In cost-effectiveness, apixaban was predicted to lead to 19 fewer strokes, 43 fewer major bleeds, 23 fewer cardiovascular related death in warfarin suitable population. In warfarin unsuitable population, apixaban was predicted to lead to 70 fewer strokes, 39 fewer major bleeds, 56 fewer CV-related deaths [25].

In Australia (2013), when patient receive warfarin therapy, it showed 7.72 years of life lived (YLL) and 5.84 QALYs at a net cost of AUD$ 24,641 per person. Apixaban therapy resulted in 8.05 YLL and 6.15 QALYs at a net cost of AUD$ 28,949 per person. Apixaban provided a 0.33 LYG and 0.31 per QALYs at an incremental cost of AUD$ 4,308 [26].

Cost-effectiveness comparison among the dabigatran to warfarin

This review identified most primary studies on examining the comparison of the cost-effectiveness of dabigatran to warfarin, which is 12 studies. Most studies were retrospective analyses reporting quality-adjusted life years (QALY), total costs, and incremental cost-effectiveness ratios (ICER). Among the 12 studies, 3 of them from the United State and the United Kingdom respectively. 2 of the studies were conducted in Netherland with each one study from Hong Kong, Ireland and Sweden.

In United State (2012), QALYS was 10.28 in warfarin, 10.70 in low dose dabigatran, and highest in high dose dabigatran, 10.84. When the ICER is compared with warfarin, low-dose dabigatran showed $51 229 per QALY and high dose dabigatran showed $45 372 per QALY [27]. Another US study (2012) suggested 4.27 QALYs in dabigatran, 3.91 QALYs in warfarin and ICER of $25 000 in dabigatran [28]. On the other hand, in 2011, dabigatran of 8.54 QALYs and warfarin of 8.40 QALYs are estimated in St. Louis [29].

While in the United Kingdom (2011), QALYs become slightly lower, only 8.06 QALYs in dabigatran) with 7.82 in warfarin and 7.59 in aspirin. ICER concluded £4831/QALY in dabigatran etexilate and £20000/QALY in warfarin [30]. On the other hand, another study (2012) suggested 0.094 QALYs in dabigatran etexilate and 0.146 QALYs in high dose of dabigatran etexilate with ICERs (€/QALY) of 23082 of dabigatran etexilate [31]. The third UK studies (2011) give 0.094 QALYs in low dose of dabigatran etexilate, 0.146 QALYS in high dose of dabigatran etexilate. ICERs of dabigatran etexilate gives £23,082/QALY [32].

The willingness to pay threshold of Netherland (2016) residents is €20,000 per QALY. The probability that dabigatran is cost-effective reach 99%. ICER is €20,000/QALY [33]. Besides that, in another Netherland study suggested 0.0349 QALYs in dabigatran with ICERs (€/QALY) of 20,000 (dabigatran) vs 2158(vitamin K antagonist) vs 33,379(no treatment) [34]. In the Sweden (2012), study reported total cost of warfarin (€24 797), dabigatran (€27,009). The number of strokes prevented by taking warfarin is lower in 0.52 and dabigatran (0.37. However, for the life years gained, dabigatran (12.11) is higher than warfarin (11.83). QALY of warfarin (8.31) and dabigatran (8.60) was reported. When dabigatran compared with warfarin-, cost per QALY is €7742 and cost per life year is €7699 [35].

A study from Hong Kong (2013) suggested ICER of US $68333 (dabigatran) and US$20500 (warfarin) [36]. By comparison, Ireland (2012) suggested QALY of 10065 on dabigatran with ICER of USD 13810 [37].

Cost-effectiveness comparison among the rivaroxaban to warfarin

Six primary studies had identified as the comparison of the cost-effectiveness of rivaroxaban to warfarin. Most outcomes are quality-adjusted life years (QALY), total costs, and incremental cost-effectiveness ratios (ICER). Each of the studies is conducted in different country which are the German, United Kingdom, Netherland, United State, Portuguese and one with unknown setting.

Quality-adjusted life expectancy in patients with non-valvular AF in the German (2014) is 11.06 QALYs when they receive rivaroxaban. When they treated with adjusted-dose warfarin, the QALYs is 10.35. The corresponding total costs were €9,464 for warfarin and €20,238 in rivaroxaban. ICER for rivaroxaban compared with warfarin is €15,207 per QALY [38].

In UK (2010), the study investigated rate of recurrence as its outcome of interest. Rivaroxaban had non inferior efficacy with respect to the primary outcome (36 events [2.1%], vs. 51 events with vitamin K antagonist [3.0%]. The hazard ratio is 0.68; 95% confidence interval [CI] ranged from 0.44 to 1.04. P<0.001). Rivaroxaban had superior efficacy (8 events [1.3%], vs. 42 with placebo [7.1%]; hazard ratio, 0.18; 95% CI, 0.09 to 0.39; P<0.001). Four patients in the rivaroxaban group had nonfatal major bleeding (0.7%), versus none in the placebo group with P of 0.11 [39].

Rivaroxaban is the better treatment option for the prevention of ischemic strokes in premenopausal women in 61% of the iteration, as reported in the Netherlands (2017) [40]. In United State (2012), total costs are $94,456 in rivaroxaban vs $88,544 in Warfarin. QALYs was 10.027 in Rivaroxaban versus 9.812 in Warfarin. Apart from that, ICERs ($/QALY) is 27,498 in Rivaroxaban) when compared to warfarin [9]. Lastly, in Portuguese (2014), the study showed although rivaroxaban gets additional cost of €81, QALYs increase 0.021 and life increase 0.023 with ICER is €3494/LY, €3895/QALY [41].

Cost-effectiveness comparison among the edoxaban to warfarin

Only 2 primary studies of comparison of cost-effectiveness of edoxaban to warfarin are identified. One of them conducted in the German while the other one is non-available setting. In the German (2015), the ICER for edoxaban 60mg was lower compared to edoxaban 30mg daily. Compared to the other NOAC regimens, edoxaban 60 mg had the lowest ICER. In the two-way sensitivity analysis, edoxaban had set willingness to pay of 50.000C per QALY against INR-dose-adjusted warfarin. In probabilistic sensitivity analyses, edoxaban 60 mg od and edoxaban 30 mg od set willingness-to-pay at threshold of 52.000C per QALY and 67.000C per QALY [42]. The other studies suggested 8.425 QALYs in warfarin and higher QALYs in edoxaban, which is 9.022 QALYs. The ICUR gained was €7,713/QALY [43].

Discussion

The objective of this review is to study the economic outcomes of application of Novel Oral Anti-Coagulants (NOAC) in patients with cardiovascular disease. The four currently available NOAC are dabigatran, rivaroxaban, apixaban and edoxaban. There are a total of 43 articles included in this systematic review study which comprise 7 articles that compare the cost-effectiveness among the NOAC, 8 articles on cost-effectiveness of NOAC compared with warfarin, and a total of 8, 12, 8 and 2 articles comparing the cost-effectiveness of apixaban, dabigatran, rivaroxaban and edoxaban, respectively, with warfarin.

When NOAC is compared with warfarin, the result shows that NOAC is more cost-effective [13-15,17-18,23, 44] despite the cost of warfarin is much cheaper than all the 4 NOAC [13,15-16,18). This can be explained from the QALYs gained for treatment with NOAC are higher than that of warfarin [13-19]. When NOAC is compared among each other, there is a study reported that dabigatran yields more total QALYs at lower lifetime costs than apixaban and rivaroxaban, thus making them conclude that dabigatran is more cost-effective than other NOAC [7]. In overall, apixaban is said to be the most cost-effective out of all NOAC where the usage of apixaban shows a reduction in medical cost [23,26] and the average survival of this drug is the highest [17,26]. Although the cost of this drug is quite high [13,15], but the QALYs gains is also relatively high [13-15].

Besides that, this review found that studies from different countries show different preferences. In the German, a study done in the year of 2014 concluded that rivaroxaban was found to be more cost-effective than warfarin with an ICER of €15,207 per QALY gained [38], whereas in 2015, a different study reported that edoxaban in addition to apixaban may be regarded as the most cost-effective NOAC [42]. There are a lot of studies done in UK starting from 2010 to the latest in 2016 and the result varies in different studies. In 2010, rivaroxaban is reported as a safe single oral anti-coagulant [39,45], whereas a different result is reported in 2011 and 2012 where dabigatran is more cost-effective to be used with the positive benefit to harm ratio value [30-32]. Another study done in 2015 reported the same result as in 2011 and 2012 where the QALYs gained is higher with lower lifetime cost [7]. Apixaban is the most cost-effective drug reported in 2014 and 2016 [21,46-48]. This phenomenon also occurs in the US where the drug reported to be the most cost-effective varies throughout the years [8,9,13,23,27,29-30,49]. But still a study done in 2016 concluded that all NOACs were more cost-effective than adjusted dosed warfarin with the value of QALY among all NOACs were close to each other [14]. In Asia region, a study done in Singapore concluded that rivaroxaban is more cost-effective alternative to warfarin for the prevention of stroke [18]; in the Japan they believed that apixaban is more cost-effective in stroke prophylaxis and Hong Kong favoured dabigatran for stroke prophylaxis compared to the current treatment.

In the treatment of atrial fibrillation and stroke prevention, most of the studies found that apixaban is the most cost-effective alternative to other NOACs and warfarin [10-12,15,21-22,24,46-47,49]. In the treatment of venous thromboembolism, apixaban also provides a superior alternative compared to other NOACs while warfarin and offers health benefits for a lower cost [25-26]. A study found that dabigatran is cost-effective compared to vitamin K antagonist in the treatment of venous thromboembolism [34]. Dabigatran and rivaroxaban are found to be more cost effective than warfarin in the treatment of pulmonary embolism [19]. A study found that both apixaban and warfarin are efficient therapy for pulmonary embolism [48].

Most of the studies reviewed show concern on the cost of drug and QALY. The economic burden in chronic conditions are not studied. Majority of cardiovascular diseases are chronic diseases such as stroke, therefore the substantial economic burden such as productivity as well as caregiver burden can be a significant concern. The lack of study in this aspect may be due to the fact that NOACs are relatively new drug and they have not been widely used worldwide. Since NOACs are quite novel, many of the economic evaluations are based on clinical trial data which may not reflect

the real-world setting. The subjects in clinical trial may receive better care while in real-world clinical setting, many other factors such as local healthcare cost, health behavior, and drug adherence may vary. In addition to that, most of the economic evaluations had a short time horizon, so the direct application of the data to the real-world setting is impractical. In term of cost, the drug cost and other medical cost vary over time and this factor is not taken into account. Whilst in term of efficacy, the long-term effect of the drug may not be noted for a short period of follow-up, let the effect be beneficial or not.

Comparing the results from cost-effectiveness analysis across different health care settings poses a big challenge as the design of economic models for analysis varies from each other. It is not appropriate to compare studies in different settings because of the differences in treatment guidelines, real-world clinical practice, country's economy, and cost estimates used to populate models. Markov model is the most used however modifications of this model are made in many studies, which causes the results may not be coherent with each other. The difference of ICER threshold also should be noted, as a different threshold value may totally alter the cost-effectiveness of a drug Table 1.

Table 1

Author	Study Design	Sample size	Inclusion /Exclusion	Outcome of interest	Conclusions
Krejczy M, et al. [16]	Markov decision model, Monte Carlo simulation	Hypothetical cohort RE-LY (18113 patients)	Inclusion: Patients with non-valvular atrial fibrillation using oral anticoagulants dabigatran, rivaroxaban and apixaban	Quality-adjusted life years (QALY), total costs, and incremental cost-effectiveness ratios (ICER).	At current market costs of the NOACs, nontherapeutic regimens seem to be cost-effective from a German public health care insurance perspective.
Zheng Y, et al. [7]	Markov model with 3-month model cycles	5990	Inclusion: Patients taking NOACs and warfarin and having diseases: acute thromboembolic and bleeding events, as well as long-term consequences of stroke, intracranial hemorrhage, and acute myocardial infarction	Cost-effectiveness	Dabigatran yields more total QALYs at lower lifetime costs than apixaban and rivaroxaban, dominating the other 2 NOACs.
Kamae I, et al. [24]	Lifetime Markov model	1000	Inclusion: Patients with non-valvular atrial fibrillation using oral anticoagulants dabigatran, rivaroxaban and apixaban	Direct medical cost, long-term care cost, and quality-adjusted life years (QALYs)	Apixaban is a cost-effective alternative to warfarin in Japan for stroke prevention among patients with NVAF.
Lip GY, et al. [46]	Markov model	rivaroxaban, n = 7131, warfarin,n = 7133	Inclusion: AF patients	Life-years, quality-adjusted life years gained, direct health care costs, and incremental cost-effectiveness ratios.	Apixaban may be a cost-effective alternative to dabigatran 150 mg BID, dabigatran 110 mg BID, and rivaroxaban 20 mg once daily for stroke prevention in AF patients.
Lanitis T, et al. [48]	Markov cohort model	1000	Inclusion: patients with atrial fibrillation taking apixaban, warfarin and aspirin	Health care costs and life-years and quality-adjusted life years	Apixaban was found to be a cost-effective alternative to warfarin and aspirin for stroke prevention in patients with AF in Sweden.
Verhoef, et al. [12]	Randomised control trial and cohort study	100	Inclusion: healthy with atrial fibrillation (AF), ischaemic stroke (IS), transient ischaemic attack (TIA), myocardial infarction (MI), SE, intracranial haemorrhage (ICH), extracranial haemorrhage (ECH), disability and death. Age-specified (70 years old)	1)Quality-adjusted life-year (QALY) values 2) Incremental cost-effectiveness ratios (ICERs)	Apixaban,Rivaroxaban and dabigatran are cost-effective alternatives to coumarin derivatives in the UK, while in the Netherlands, only apixaban and dabigatran could be considered cost effective.
Ye Wang, et al. [18]	Markov model	Hypothetical cohort	Inclusion: Anticoagulation, Atrial fibrillation, Cost-effectiveness, Dabigatran, Rivaroxaban, Warfarin	Direct medical costs, Quality-adjusted life years (QALYs)	Rivaroxaban may be a cost-effective alternative to warfarin for the prevention of stroke in patients with AF in Singapore.
Andrej Janzic, et al. [17]	Cohort study	18112 patients	Inclusion: Nondisabled, 70-year-old patients with increased risk for stroke who started anticoagulation treatment. Four additional health states were defined: nondisabled and on treatment; disabled and on treatment; disabled and off treatment; and nondisabled and off treatment. Patients at any health state were at risk for ischaemic stroke, systemic embolism, myocardial infarction, intracranial haemorrhage and other major haemorrhage.	1) Quality-adjusted life-years (QALYs) 2) Incremental cost-effectiveness ratio (ICER) for each NOAC, compared with warfarin treatment.	NOACs were cost-effective alternatives to warfarin at TTR up to 65 % however at better warfarin control, the ICERs of NOACs were higher, indicating that warfarin was the preferred treatment.

Alexander Mensch, et al. [38]	Randomised control trial and cohort study	Unclear	Inclusion: Patients aged 65 years with non-valvular AF and without contraindications to anticoagulation who were at moderate to high risk of stroke.	Quality adjusted life years (QALYs)	Treatment with rivaroxaban was found to be more effective than warfarin treatment, with an ICER of €15,207 per QALY gained favoring rivaroxaban.
Gregory YHLip, et al. [47]	Cohort study	1000 patients (100 patients per year)	Inclusion: Cohort of patients with the condition over a lifetime horizon. NVAF without complications, NVAF with stroke or NVAF with bleeding	Mean life-years (LYs) Quality-adjusted life-years (QALYs) Costs per patient. Incremental cost effectiveness ratio (ICER) of a currency (euro, USD, or any other currency) per quality adjusted life years (QALY).	The comprehensive assessment of the long-term efficacy, safety, and tolerability profile of apixaban in this study, generated through means of an economic model, predicted that the drug would provide an attractive alternative to other NOACs in the prevention of thrombo embolic events in patients with AF.
Martin Krejczy, et al. [42]	Randomised control trial and cohort study	Hypothetical cohort ENGAGE-AF (21,105 patients) RELY (18,113 patients), ROCKET (14,264 patients), ARISTOTLE trials (18,201 patients)	Inclusion: Healthy with NVAF, transient ischemic attack, ischemic stroke (fatal, moderate to severe, and mild), haemorrhage (fatal, moderate to severe intracranial, mild intracranial, major noncerebral, and minor noncerebral), myocardial infarction (MI), recurrent and combined events, and cardiovascular mortality using the results from the ENGAGE-AF trial and costs.		Edoxaban in addition to apixaban may be regarded as the most cost-effective NOAC from a German public health care insurance perspective.
Zanfina Ademi, et al. [11]	Cohort study	1000	Inclusion: AF or flutter and at least one of the following risk factors: age of at least 75 years; previous stroke, transient ischaemic attack (TIA) or systemic embolism; symptomatic heart failure within the previous three months or left ventricular ejection fraction (LVEF) of no more than 40%; diabetes mellitus; and hypertension requiring pharmacologic treatment.	Life per gained (LYG) and quality adjusted life years (QALYs)	Compared to warfarin, apixaban is likely to represent a cost-effective means of preventing stroke-related morbidity and mortality in patients with AF.
Soyon et al. [9]	Markov model	Hypothetical cohort	Inclusion: Cost effectiveness, apixaban, stroke, atrial fibrillation	Costs in 2012 US$, quality-adjusted life-years (QALYs), life years saved, incremental cost-effectiveness ratios	In patients with AF and at least one additional risk factor for stroke,treatment with apixaban may be a cost-effective alternative to warfarin.
Martin Krejczy, et al. [42]	Markov model	1000	Inclusion: Stroke, apixaban, cost-effectiveness, atrial fibrillation, new oral anticoagulant.	LYs, QALYs, and costs accumulated	Apixaban may be a cost-effective alternative to dabigatran 150 mg BID, dabigatran 110 mg BID, and rivaroxaban 20 mg once daily for stroke prevention in AF patients from the perspective of the United Kingdom National Health Services
Tereza Lanitis, et al. [20]	Markov model	1000	Inclusion: Cost effectiveness, apixaban, anticoagulants, venous thromboembolism,	Number of events avoided in 1000 cohort patients, Total costs, Life years, QALYs (Quality Adjusted Life Years), Cost per QALY gained over a patient's lifetime	Apixaban would provide a superior alternative to other NOACs in terms of the initial treatment of VTE and prevention of recurrences as well as reduction in bleeding events over 6 months of treatment, offering favourable health benefits for a lower cost.
Paul Dorian, et al. [21]	Markov cohort model	1000	Inclusion: Aspirin, Stroke prevention, Apixaban, Cost-effectiveness, Atrial fibrillation	Life expectancy, Quality-adjusted life years (QALYs)	Based on randomized trial data, apixaban is a cost-effective alternative to warfarin and aspirin, in VKA suitable and VKA unsuitable patients with AF, respectively.
Amanda R Harrington, et al. [13]	Markov decision-analysis model	Hypothetical cohort	Inclusion: Anticoagulation, atrial fibrillation, cost-effectiveness	Costs, QALYs, and ICERs, Willingness to Pay	In patients with nonvalvular atrial fibrillation and an increased risk of stroke prophylaxis, apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg were all cost-effective alternatives to warfarin.

Merlijn W J van Leent, et al. [33]	A retrospective observational study	dabigatran (2553) warfarin (2554)	Inclusion: Cost effectiveness, Dabigatran	QALYs, ICER	Inserting these real-world data into a cost-effectiveness analysis for patients diagnosed with DVT, dabigatran appeared to be a cost-saving alternative to VKAs in the Netherlands in the base case.
Thomas Davidson, et al. [35]	A decision analytic simulation model following a Markov design	Hypothetical cohort RE-LY (18 113 patients)	Cost effectiveness, atrial fibrillation and anticoagulants.	number of strokes prevented, life years gained, quality-adjusted life years (QALYs) gained	Dabigatran is a cost-effective treatment in Sweden, as its incremental cost-effectiveness ratio is below the normally accepted willingness to pay limit.
James V Freeman, et al. [27]	Markov decision model.	Hypothetical cohort RE-LY (18 113 patients)	Cost effectiveness, Warfarin, Dabigatran, Atrial Fibirlation, Stroke	Quality-adjusted life-years (QALYs), Costs (in 2008 U.S. dollars), Incremental cost-effectiveness ratios	In patients aged 65 years or older with nonvalvular AF at increased risk for stroke (CHADS2 score 1 or equivalent), dabigatran may be a cost-effective alternative to warfarin depending on pricing in the United States.
Hooman Kamel, et al. [28]	Randomized controlled trial and Cohort study	Hypothetical cohort	Inclusion:Patients with nonvalvular atrial fibrillation, prior stroke or transient ischemic attack, and no contraindication to anticoagulation. Exclusion: Patients with disability, ischemic stroke, intracerebral hemorrhage, recurrent orcombined stroke and/or intracerebral hemorrhage, and death	QALY, ICER	Dabigatran is likely to be a cost-effective alternative to warfarin for stroke prevention in typical patients with atrial fibrillation who have had a stroke or transient ischemia attack.
Andy M Chang, et al, [36]	Markov Model	244	Inclusion: Patients with non-valvular atrial fibrillation taking dabigratan and warfarin	Incremental cost-effectiveness ratio (ICER).	Dabigratan is favored for stroke prophylaxis in patients with non-valvular atrial fibrillation in Hong Kong under the current hospital's perspective and provided a reference for further comparisons under patient and subsidization perspectives.
Anuraag R Kansal, et al. [30]	Markov Model	Hypothetical cohort RE-LY (18 113 patients)	Inclusion:Patients with atrial fibrillation taking dabigatran etexilate and warfarin and aspirin	Quality-adjusted life years (QALY), Incremental cost-effectiveness ratio(ICER)	Patients with atrial fibrillation will be having more cost-effective with the use of dabigratan etexilate as a first-line treatment for prevention of stroke and systemic embolism.
Shimoli V Shah, et al. [29]	Markov model	Hypothetical cohort RE-LY (18 113 patients)	Inclusion: Patients with atrial fibrillation taking dabigratan and warfarin	Quality-adjusted life years (QALY)	Dabigratan is more cost-effective in atrial fibrillation populations at high risk of hemorrhage or high risk of stroke whereas warfarin is more cost-effective in moderate-risk of atrial fibrillation populations.
Joyce HS You, et al. [37]	Markov model	18000	Inclusion: Patients with atrial fibrillation taking dabigratan	Qality-adjusted life-year (QALY) and Incremental cost-effectiveness ratio(ICER)	Genotype-guided anticoagulation service to be accepted as cost-effective would increase if the quality of life on warfarin and dabigratan therapy are compatible and genotype-guided service achieves high TTR.
Doug Coyle, et al. [15]	Markov cohort model	Hypothetical cohort RE-LY (18,113 patients) ROCKET (14,264 patients) ARISTOTLE trials (18,201 patients)	Inclusion: Patients with non-valvular atrial fibrillation taking dabigratan,rivaroxaban,apixaban and warfarin	Quality-adjusted life-year (QALY) , Cost, Incremental cost per QALY gained(-ICUR)	Rivaroxaban and dabigratan (110mg) are unlikely to be cost-effective whereas apixaban and dabigratan (150mg) are optimal.
Anuj Shah, et al. [14]	Cohort Studies	10000	Inclusion:Patients with ICH, myocardial infarction (MI), stroke, and ECH. Exclusion: Unclear	QALY, Cost effective, Incremental cost-effectiveness ratio(ICER)	All the NOACs we compared were more effective than adjusted dosed warfarin; however, the QALY among all NOACs was similar.

William J Canestaro, et al. [22]	Randomized controlled trial and Cohort study	Hypothetical cohortRE-LY (18,113 patients) ROCKET (14,264 patients)ARISTOTLE trials (18,201 patients)	Inclusion: Patients that are newly diagnosed atrial fibrillation who were eligible for treatment with warfarin. Exclusion: Unclear	Incremental cost-effectiveness ratios	Although all the novel oral anticoagulants produce greater quality-adjusted life expectancy than warfarin, they may not represent good value for money.
Torbjørn Wisløff, et al. [44]	randomized clinical trials (RCT)	Unclear	Unclear	ICER	Apixaban and dabigatran (150 mg up to age 80 years, 110 mg after age 80 years) seem to be the most effective and cost-effective alternatives.
Carla Rognoni, et al. [43]	randomized clinical trials (RCT)	Unclear	Unclear	QALY Incremental cost-utility ratio (ICUR)	Edoxaban resulted cost-effective versus warfarin in 92.3 % of the simulations using a willingness-to-pay threshold of €25,000 per QALY and in 96 % of the simulations using a willingness-to-pay threshold of €50,000 per QALY
Andreas Clemens, Siyang Peng, Sarah Brand, 2014	Cohort	Hypothetical cohortRE-LY (18 113 patients)	Unclear	Clinical event costs avoided cost-effectiveness	Dabigatran was cost-effective versus warfarin in US patients with atrial fibrillation regardless of age of treatment initiation
Alpesh Amin, et al. [23]	randomized clinical trials (RCT)	RE-SONATE (4199 patients) EINSTEIN-EXT (3449 patients) AMPLIFY-EXT (2486 patients)	Unclear	Medical cost avoidance	Apixaban is associated with the greatest medical cost avoidance, which is driven mainly by a greater reduced rate in recurrent VTE than other NOACs versus placebo and also a reduction in MB rate.
Alpesh Amin, et al. [23]	randomized clinical trials (RCT)	23,525	Unclear	Total medical cost	Apixaban and dabigatran are more cost-effective compared with warfarin while warfarin is more cost-effective than rivaroxaban.
Bauersachs R, et al. [45]	randomized clinical trials (RCT)	4646	Inclusion: Acute, symptomatic, objectively confirmed proximal DVT, without symptomatic pulmonary embolism. Exclusion: received therapeutic doses of low-molecular-weight heparin, fondaparinux, or unfractionated heparin for more than 48 hours or if they had received more than a single dose of a vitamin K antagonist before randomization	Rate of recurrence	Oral rivaroxaban provide an effective,
Büller HR, et al. [39]	randomized clinical trials (RCT)	4832	Exclusion: indication for a vitamin K antagonist; a creatinine clearance below 30 ml per minute; clinically significant liver disease or an alanine aminotransferase level that was more than three times the upper limit of the normal range; bacterial endocarditis; active bleeding or a high risk of bleeding contraindicating anticoagulant treatment; a systolic blood pressure of more than 180 mm Hg or a diastolic blood pressure of more than 110 mm Hg.	A fixed-dose regimen of rivaroxaban alone was non inferior to standard therapy for the initial and long-term treatment of pulmonary embolism and had a potentially improved benefit-risk profile	The use of rivaroxaban as a single oral agent for patients with venous thromboembolism is effective
Lanitis T, et al. [48]	Cohort study	Hypothetical cohort 1000 patients	Unclear	An economic evaluation of the currently prescribed treatments for stroke prevention in patients with NVAF including warfarin, aspirin and NOAC from French payer perspective	The efficiency frontier approach demonstrated that warfarin and apixaban are efficient therapies in terms of cost, QALYs, and subsequent efficiency for patients with AF in France.

Vivek Y Reddy, et al. [19]	Markov model	Ruff et al., 2014 (71 683 patients) Holmes et al., 2009 (707 patients), [38] Hart et al., 2007 (28 044 patients) Pisters et al., 2010 (3978 patients) Connelly et al., 2009 (18,113 patients)	Inclusion: Acute, symptomatic, objectively confirmed proximal DVT, without symptomatic pulmonary embolism. Exclusion: received therapeutic doses of low-molecular-weight heparin, fondaparinux, or unfractionated heparin for more than 48 hours or if they h Data related to aspirin and clopidogrel	The cost-effectiveness and QALY of warfarin, NOACs, and LAAC for stroke risk reduction in patients with nonvalvular AF.	Both novel therapies demon-strated cost-effectiveness relative to warfarin, but only LAAC demonstrated cost savings by year 10 relative to warfarin and by year 5 relative to NOACs.
Herbert JA, et al. [40]	Markov model	1000	Inclusion: Acute, symptomatic, objectively confirmed proximal DVT, without symptomatic pulmonary embolism. Exclusion: received therapeutic doses of low-molecular-weight heparin, fondaparinux, or unfractionated heparin for more than 48 hours or if they h	Associated quality adjusted life years, and health care costs of Rivaroxaban and VKAs	Although RVX seems promising, there is still uncertainty on whether RVX or VKAs should be prescribed in premenopausal women, mainly because of the uncertainty on the risk of AUBs and ischemic strokes.
Soyon Lee, et al. [8]	Markov modeling	Hypothetical cohort 1000 patients	Inclusion:Patients of atrial fibrillation taking rivaroxaban and warfarin.	1)Costs in 2011 United States dollars	Rivaroxaban may be cost-effective alternative to warfarin in patients with atrial fibrillation regardless of baseline ischemic stroke risk.
Morais J, et al. [41]	Markov modeling	Hypothetical cohort ROCKET AF clinical trials (14,000 patients)	Inclusion: Acute, symptomatic, objectively confirmed proximal DVT, without symptomatic pulmonary embolism. Exclusion: received therapeutic doses of low-molecular-weight heparin, fondaparinux, or unfractionated heparin for more than 48 hours or if they h	1)Incremental Life Years (LYs) 2) Quality-Adjusted Life Years(QALYs) 3)Incremental cost-effectiveness ratios(ICERs) 4)Incremental costs	Rivaroxaban is cost-effective compared with vitamin K antagonist therapy in a trial-based setting, and also compared to real-world antithrombotic prescribing in Portugal for stroke prophylaxis in patients with atrial fibrillation.
Anuraag R Kansal, et al. [30]	Markov modeling	Hypothetical cohort RE-LY (18 113 patients)	Inclusion:Patientswith atrial fibrillation takingDabigatran etexilate,warfarin, aspirinandno therapy	1)Quality-adjusted life years(QALYs) 2)Incremental cost per QALY	Dabigatran offers a positive benefit to harm ratio when compared with warfarin.
J Stevanoic, et al. [34]	Markov modeling	10,000 adult patients RE-LY (18 113 patients)	Inclusion: Patients with venous thromboembolism taking dabigratan	1)Quality-adjusted life years (QALYs) 2)Incremental cost-effectiveness ratio(ICER)	Dabigatran is likely to be a cost-effective or even cost-saving strategy for treatment and secondary prevention of venous thromboembolism compared to vitamin K antagonists in the Netherlands.
Joshua Pink, et al. [32]	Markov modeling	50,000	Inclusion: Patients with non- valvular atrial fibrillation taking dabigratanetexilate and warfarin	1)Quality-adjusted life years (QALYs) 2) Incremental cost per QALY	Dabigatran offers a positive benefit to harm ratio when compared with warfarin.

There were several limitations in this systematic review. The differences in healthcare system across countries and the study designs making it not possible to compare results of economic models that are adopted from different perspectives. Additionally, differences in patients' health states, adherence to medication and healthcare resource use where the economic models did not take account of. This variability did not reflect real-world clinical practices. The economic models used are adopted across various time horizons, with many of the models estimating cost over 3 months to 1 year. A careful consideration should be paid to the selection of appropriate time horizons for future models.

Conclusions

Numerous studies investigated novel oral anticoagulants (NOACs), namely, apixaban, edoxaban, rivaroxaban and dabigatran, since they were introduced to clinical practice, especially for their various roles in management of cardiovascular diseases. With proven NOAC clinical superiority and the lower need of follow-up visits and lab tests, NOAC economic profile is a broad area of research. The current study managed to review 43 studies investigating NOACs based on the inclusion criteria. The review investigated studies that emphasized on QALYs, total costs and incremental cost-effectiveness ratios (ICER) and willingness to pay. Despite

the variations in quality, sampling, design of studies investigating NOACs, all studies reported that NOAC are more cost-effective than warfarin in terms of indirect costs and quality-adjusted life year (QALYs). Generally, among NOAC, dabigatran is more cost-effective than apixaban, rivaroxaban and edoxaban as it yields more total QALYs at lower lifetime costs. Nonetheless, apixaban is the most cost-effective among all NOACs in the treatment of atrial fibrillation, stroke prevention, and venous thromboembolism. However, the comparison between NOACs in the treatment of pulmonary embolism was less conclusive, which is an open are of research for future studies evaluating economic profile of NOAC with pulmonary embolism. Besides that, further research is also needed to assess the impact of the reduction in economic burden for a more holistic pharmacoeconomic evaluation of NOAC.

Acknowledgment

The author would like to acknowledge Universiti Sains Malaysia, School of Pharmaceutical Sciences for providing the facilities and resources to ease the access of databases.

Conflict of Interest

No conflict of interest.

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