

SUPPLEMENTARY MATERIAL

Appendix 1. Table summarizing the main information of the 26 selected articles in this study.

Reference	Country	Comparators	Perspective	Time Horizon	Type of analysis	ICER results	Sensitivity analysis	Conclusions
[10]	Argentina	Apixaban vs. warfarin	Payer	Lifetime	CEA/CUA Markov model	USD 823.29/LYG USD 786.08/QALY USD 5,422.01/Stroke avoided USD 3,268.66/Bleed avoided	<ul style="list-style-type: none"> • Apixaban is a CE alternative in 90% of cases • One way SA: the risk of stroke with apixaban is the main contributor to the CE • SA apixaban vs. acenocoumarol = USD 711.52/QALY 	Using local epidemiological estimates and based on randomized clinical trial data, apixaban turned out to be a CE alternative to warfarin according to local willingness-to-pay thresholds.
[11]	Slovenia	Warfarin (genotype-guided dosing), dabigatran, rivaroxaban, apixaban and edoxaban vs. standard warfarin	Payer	Lifetime	CUA Markov model	Guided: €6,959/QALY Dabi: €16,959/QALY Riva: €66,328/QALY Apixa: €15,679/QALY Edoxa: €18,994/QALY	<ul style="list-style-type: none"> • Univariate sensitivity analysis demonstrated that efficacy and cost parameters of NOACs had the greatest impact on results. • The probabilistic-sensitivity analysis of the base case showed that apixaban, dabigatran, edoxaban and rivaroxaban were cost-effective options in 57%, 28%, 14% and <1%. Treatment with warfarin was cost-effective in 49% of iterations when a TTR of 70% was applied. 	The cost-effectiveness of NOACs for stroke prevention in NVAF patients with increased risk of stroke was sensitive to warfarin anticoagulation control. NOACs were cost-effective alternatives to warfarin at TTRs of up to 65%. At better warfarin control, the ICERs of NOACs were higher, indicating that warfarin was the preferred treatment.

[12]	Belgium	Warfarin vs. apixaban, dabigatran 110 mg, dabigatran 150 mg, rivaroxaban	Payer	Lifetime	CUA Markov model	Dabi 110: €13,564/QALY Dabi 150: €7,585/QALY Riva: €7,765/QALY Apixa: €7,212/QALY	<ul style="list-style-type: none"> • The deterministic analysis highlighted that dabigatran 110 mg was dominated by dabigatran 150 mg and rivaroxaban, both extendedly dominated by apixaban. • At thresholds above €10,000, apixaban had the highest probability of being the optimal treatment of choice. Dabigatran 110 mg, dabigatran 150 mg, rivaroxaban and apixaban have a probability of being the optimal treatment choice of 0%, 1%, 8%, 9% and 82%, respectively. 	In conclusion, apixaban appears to be the most economically justifiable oral anticoagulant (OAC) offering additional health benefits over other OACs, at an acceptable cost for health payers according to current standards of willingness to pay.
[13]	Spain	Apixaban vs. rivaroxaban	Payer and societal	Lifetime	CEA/CUA Markov model	€1,855/LYG (NHS) €2,347/QALY (NHS) Dominant (societal)	<ul style="list-style-type: none"> • Deterministic sensitivity analysis: Varying the most sensitive parameters did not affect the results. • According to the probabilistic sensitivity analysis, the probability of apixaban being cost-effective against rivaroxaban would be 91.7%. 	Apixaban is a cost-effective treatment compared to rivaroxaban in preventing stroke in NVAf patients, applying the generally accepted cost-effectiveness threshold in Spain.

[14]	Spain	Apixaban vs. Acenocoumarol	Payer and societal	Lifetime	CEA/CUA Markov model	€13,305/LYG (NHS) €9,765/LYG (societal) €12,765/QALY (NHS) €9,412/QALY (societal)	<ul style="list-style-type: none"> • Sensitivity analyses confirmed that apixaban is a cost-effective treatment against warfarin. Varying the study's most sensitive parameters did not affect the results. • According to the probabilistic sensitivity analysis, the probability that apixaban is cost-effective versus acenocoumarol is 87%. 	Apixaban may be a cost-effective treatment compared to warfarin with a high probability (87%). The stability of the results of the base case analysis has been confirmed in the deterministic and probabilistic sensitivity analyses.
[15]	Spain	Apixaban vs. dabigatran	Payer and societal	Lifetime	CEA/CUA Markov model	<p>Vs. dabigatran 110 mg €1,103/LYG (NHS) €1,299/QALY (NHS) Dominant (societal)</p> <p>Vs. dabigatran 150 mg €5,571/LYG (NHS) €6,591/QALY (NHS) €9,024/LYG (societal) €10,676/QALY (societal)</p>	<ul style="list-style-type: none"> • Deterministic sensitivity showed that varying the most sensitive parameters did not affect the results. • According to the probabilistic sensitivity analysis, apixaban is likely to be cost-effective in 99.3% of cases compared to the low dose of dabigatran and in 91.6% of cases compared to the high dose. 	Apixaban is a cost-effective treatment compared to dabigatran for stroke prevention in NVAF patients, according to the threshold generally accepted in Spain.

[16]	UK	Dabigatran vs. apixaban, rivaroxaban and warfarin	Payer	Lifetime	CEA/CUA Markov model	Dabigatran dominant vs. rivaroxaban, apixaban and warfarin	<ul style="list-style-type: none"> • The most significant driver of cost-effectiveness was the RR of IS. • The most cost-effective treatment option was dabigatran in 92% of the model runs and apixaban in 8% of the model runs, whereas rivaroxaban and warfarin were not the most cost-effective treatments at this WTP in any of the model runs. 	This study provided a meaningful comparison of the relevant treatments for AF in the UK, a field that has recently become crowded with multiple new treatment options. The results of this analysis indicated that dabigatran yields more total QALYs at lower lifetime costs than apixaban and rivaroxaban, dominating the other 2 NOACs.
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[17]	Netherlands and UK	Apixaban, rivaroxaban, and dabigatran compared with coumarin derivatives	Payer	Lifetime	CEA/CUA Markov model	<p>The Netherlands: Riva: Dominated Apixa: €13,024/QALY Dabi: €14,626/QALY UK: Riva: Dominated Apixa: Dominated Dabi: €11,172/QALY The costs per LYG of rivaroxaban, apixaban, and dabigatran were €58,835, €14,117, and €15,860, respectively, in the Netherlands and €18,420, €11,300, and €11,029 in the UK.</p>	<ul style="list-style-type: none"> • In the Netherlands, the percentage time in range (varied from 63% to 89%) had the largest impact on the cost-effectiveness results for all three new oral anticoagulants. This parameter had a smaller impact in the UK. • In the probabilistic sensitivity analysis, the NOACs were more costly and more effective than coumarins in the majority of the simulations. 	<p>In the UK, apixaban, rivaroxaban and dabigatran appear to be cost-effective alternatives to warfarin, increasing health at acceptable costs. While all three new oral anticoagulants also lead to improved health in the Netherlands, the incremental costs of rivaroxaban are higher than what may be regarded as acceptable. Dabigatran and apixaban seem to be cost-effective options in the Netherlands. In both countries, the use of NOACs will impact the health care budget. Also, the use of anticoagulation clinics might decrease when the new drugs are used more frequently. Whether it is better to spend the budget on NOACs or on improving the quality of current care with coumarin derivatives is an interesting question for debate.</p>
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[18]	Belgium	Apixaban vs. aspirin	Payer	Lifetime	CUA Markov model	€7,334/QALY	<ul style="list-style-type: none"> • The ICERs from all scenarios varied from €3,760 to €14,082 per QALY. • Apixaban was a cost-effective alternative to aspirin in 97% of the iterations. 	Apixaban has demonstrated an advantage over aspirin with regards to the prevention of stroke events and gain in QALYs among patients in Belgium with AF who decline or cannot tolerate VKA treatment. Also, these added benefits appear to be achieved at a reasonable additional cost.
[19]	Netherlands	Apixaban vs. VKAs	Payer	Lifetime	CEA/CUA Markov model	ICER of €10,576 per QALY gained or €10,529 per LYG	<ul style="list-style-type: none"> • The uncertainty around the absolute stroke risk under apixaban, the risks of treatment discontinuations under both apixaban and VKA and the risk of ICH under VKA, showed the highest impact on uncertainty in the estimated ICERs. • The ellipsoid shape of the incremental CE plane indicated a negative correlation between incremental costs and incremental effects. • Apixaban was cost-effective at alternative WTP thresholds of €20,000/QALY and €30,000/QALY in 68% and 72% of simulations, respectively. 	In patients with non-valvular AF, apixaban is likely to be a cost-effective alternative to VKAs in the Netherlands.

[20]	Sweden	Apixaban vs. warfarin and aspirin	Societal	Lifetime	CUA Markov model	Warfarin: SEK 41,453/QALY Aspirin: SEK 41,453/QALY	<ul style="list-style-type: none"> • The comparison between apixaban and warfarin in all scenarios resulted in ICERs that varied between being dominant and SEK 79,652, mostly influenced by assumptions surrounding monitoring costs and the disutility associated with warfarin use. • Apixaban had a higher probability of being cost-effective compared with warfarin or aspirin when the willingness-to-pay was approximately SEK 35,000 for the warfarin-suitable population, and SEK 45,000 for the warfarin-unsuitable population. 	Apixaban is an economically justifiable alternative for a cohort of NVAF patients, with an average age of 70, receiving care in Sweden. It offers additional health benefits over warfarin and aspirin at an acceptable cost for health payers.
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[21]	France	Aspirin, apixaban, dabigatran and rivaroxaban vs. warfarin	Payer	Lifetime	CUA Markov model	Aspirin, dabigatran and rivaroxaban were dominated by warfarin. Apixa: €12,227/QALY	<ul style="list-style-type: none"> • The ICER of apixaban vs. warfarin varied between €5,188 and €24,792/QALY gained and was most influenced by the risk of ischemic stroke for apixaban, the risk of ICH for warfarin, and the risk of CV hospitalization for apixaban. • When comparing apixaban to warfarin only, the CEAC indicated that, at a threshold of €30,000, the probability of apixaban being the most cost-effective strategy was 85%. 	The efficient frontier approach demonstrated that warfarin and apixaban are efficient therapies in terms of cost, QALYs and subsequent efficiency for patients with AF in France. Aspirin, dabigatran and rivaroxaban were all under the efficient frontier, which means that these drugs did not provide the most cost-effective option. Based on indirect treatment comparisons, the analyses demonstrated apixaban's value as an economically justifiable alternative to the other OAC treatments.
[22]	Norway	Dabigatran, apixaban and rivaroxaban vs. warfarin	Payer	Lifetime	CUA Markov model	Sequential Dabi: €15,920/QALY Apixa: €18,955/QALY Riva: €29,990/QALY Dabi 110 mg: €66,121/QALY	<ul style="list-style-type: none"> • Model was sensitive to the cost of the drugs • No PSA 	Apixaban and dabigatran seem to be the most effective and cost-effective alternatives. Warfarin can only be a cost-effective alternative in Norway if the threshold for cost-effectiveness is much lower than that assumed.

[23]	UK	Apixaban vs. warfarin and aspirin	Payer	Lifetime	CUA Markov model	Warfarin: £11,909/QALY Aspirin: £7,196/QALY	<ul style="list-style-type: none"> • The ICERs were most favorable in high-risk patients. • Apixaban was considered to be a cost-effective treatment representing maximum net benefit over warfarin in 93% of the trials and in 99% of the trials when compared with aspirin. 	Our analysis demonstrates that apixaban, when compared with the current standard of care, provides a cost-effective alternative for the prevention of thromboembolic events.
[24]	UK	Apixaban vs. dabigatran 110 mg, dabigatran 150 mg and rivaroxaban	Payer	Lifetime	CUA Markov model	Dabi 110: £4,497/QALY Dabi 150: £9,611/QALY Riva: £5,305/QALY	<ul style="list-style-type: none"> • Sensitivity analyses for the top 15 parameters that had the largest effect on the ICERs • Probabilistic sensitivity analysis demonstrated that apixaban was more effective at a small additional cost versus other NOACs over a lifetime horizon. 	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 thromboembolic events in patients with AF. Specifically, it could offer favorable health benefits for a marginal increase in costs. In an economic environment of constrained health care resources, we believe that the findings of this study may help UK payers in making informed decisions that are in the best interests of NVAF patients.

[25]	Germany	Dabigatran, rivaroxaban and apixaban vs. warfarin	Payer	20 years	CUA Markov model	Dabi 110 mg: €294,349/QALY Dabi 150 mg: €163,184/QALY Riva: €133,926/QALY Apixa: €57,245/QALY	<ul style="list-style-type: none"> • In the SA, the key variables were drug costs, utilities for drugs, and risk of stroke and major bleeding for warfarin and NOACs. • Dabigatran 110 mg was cost-effective at a WTP threshold of €278,000/QALY and above, dabigatran 150 mg at €175,500/QALY and above, rivaroxaban at €136,500/QALY and above, and apixaban at €60,500/QALY and above. 	At the NOAC current market costs, no therapeutic regimen seems to be cost-effective from a German public health care insurance perspective. The larger reduction in medical cost due to apixaban was mainly driven by reductions in the risks for ischemic stroke and major bleeding events as compared to the two doses of dabigatran and rivaroxaban. Data on the real-life use of NOACs for preventing embolic events in NVAF patients should be generated to identify the cost-effectiveness in clinical practice for Germany and other countries.
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[26]	UK	Warfarin, warfarin (pharmacogenetic-guided), dabigatran, rivaroxaban and apixaban	Payer	Lifetime	CUA Discrete-event simulation model	Rivaroxaban was dominated by dabigatran and apixaban. Dabigatran was extensively dominated by apixaban. Genotype-guided warfarin vs. warfarin: £13,226/QALY, and for apixaban vs. genotype-guided warfarin: £19,858/QALY.	<ul style="list-style-type: none"> • ICERs were most sensitive to changes in stroke rates, vascular death rates, and the duration of treatment benefits. • The PSA indicates that apixaban has the highest probability of being cost-effective at thresholds of £13,703/QALY or above. • Scenario analyses: Among the subgroups analyzed, the mean net health benefits consistently showed the same ordering as the base case analysis. 	The analysis suggests that apixaban is the most cost-effective treatment as compared with warfarin and genotype-dosed warfarin, dabigatran and rivaroxaban.
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[27]	Italy	Apixaban vs. warfarin and aspirin	Payer	Lifetime	CEA/CUA Markov model	Against aspirin and warfarin €5,600/QALY and €5,800/LYG and €6,800/QALY and €6,200/LYG.	<ul style="list-style-type: none"> • The most influential parameters are the absolute CV risks for both treatments and the ICH risk associated with warfarin use. In any tested case, the corresponding ICER remains below commonly accepted WTP values. The same considerations hold true for the comparison against ASA, where ICER is most influenced by variations in the attributed stroke risks for both treatments, and by the level of CV risk for apixaban-treated patients. • Apixaban is expected to be a better choice than warfarin for any WTP above around €10,000/QALY, with probabilities of being cost-effective of 93% and 96%, for the conventional WTP thresholds of €20,000 and €30,000/QALY, respectively. Corresponding percentages for the comparison with aspirin in the VKA-unsuitable population are 95% and 98%. 	The clinical data and expected pharmacoeconomic performance of apixaban is favorable, and it can be considered a welcome new entry in the therapeutic armamentarium at the disposal of the physician caring for NVAf patients in Italy.
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[28]	Australia	Apixaban vs. warfarin	Payer	Lifetime	CEA/CUA Markov model	AUD 12,914/LYG and AUD 13,679/QALY	<ul style="list-style-type: none"> • One-way sensitivity analyses showed that the results were sensitive to the price of apixaban, efficacy measures from ARISTOTLE, and time frame. • Monte Carlo simulation showed that apixaban was cost-effective in over 99% of 10,000 iterations. 	Compared to warfarin, apixaban is likely to represent a cost-effective way of preventing stroke-related morbidity and mortality in patients with AF.
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[29]	US	Dabigatran, rivaroxaban and apixaban vs. warfarin	Societal	Lifetime	CUA Markov model	Dabi, Riva and Apixa: USD 140,557, USD 111,465, and USD 93,062/QALY	<ul style="list-style-type: none"> • Although apixaban was the optimal strategy at a conventional cost-effectiveness threshold, this finding was sensitive to assumptions about treatment efficacy, risks, patient demographics and drug costs. • Warfarin, apixaban, and rivaroxaban would become equivalent if the efficacy of apixaban were 3% less than assumed and if the efficacy of rivaroxaban were 5% greater than assumed. • Although apixaban seems optimal in the base case, it seems virtually indistinguishable from warfarin in the probabilistic analysis. Dabigatran and rivaroxaban were the optimal strategy in a minority of simulations and were virtually indistinguishable across the entire willingness-to-pay range evaluated. 	<p>At a standard cost-effectiveness threshold, apixaban seems to be the optimal anticoagulation strategy; this finding is sensitive to assumptions about its efficacy and cost. Interestingly, apixaban was indistinguishable from warfarin in the probabilistic analysis, suggesting that while efficacious and comparatively safe, this agent may not represent a good value for the money.</p> <p>Furthermore, it seems unlikely that rivaroxaban or dabigatran would be cost-effective at their currently assumed prices.</p>
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[30]	Italy	Dabigatran, rivaroxaban and apixaban vs. warfarin	Payer	Lifetime	CUA Markov model	<p>CHADS₂≤1, apixaban and dabigatran, €9,631 and €7,320/QALY</p> <p>CHADS₂=2, apixaban, dabigatran and rivaroxaban, €9,660, €7,609 and €20,089/QALY.</p> <p>In CHADS₂≥3, apixaban, dabigatran and rivaroxaban, €4,723, €12,029 and €13,063/QALY.</p>	<ul style="list-style-type: none"> • Results were sensitive to the time in the (warfarin) therapeutic range and time horizon. • The probabilistic sensitivity analysis confirmed that apixaban, dabigatran and rivaroxaban were cost-effective versus warfarin in 94.8%, 96.2% and 71.1% of simulations, respectively. 	<p>The results for the Italian health care system are similar to other European countries, confirming a good cost-effectiveness profile for NOACs. However, the residual uncertainty surrounding outcome estimates, also observed with other studies, supports the need for further investigations aimed at finding the most efficient and sustainable prescription strategy for NOACs.</p>
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[31]	Canada	Dabigatran 150 mg and 110 mg, rivaroxaban, and apixaban vs. warfarin	Payer	Lifetime	CUA Markov model	Dabigatran 150 mg vs. warfarin: CAD 20,797/QALY. Dabigatran 110 mg, apixaban, and rivaroxaban were dominated by dabigatran 150 mg.	<ul style="list-style-type: none"> • Results were sensitive to the drug costs of apixaban, the time horizon adopted, and the consequences from major and minor bleeds with dabigatran. • The probabilistic sensitivity analysis highlights the uncertainty around conclusions relating to cost-effectiveness. At a WTP of CAD 50,000/QALY, dabigatran 150 mg was the optimal treatment in 50.8% of the replications, apixaban in 44.1%, rivaroxaban in 2.1%, dabigatran 110 mg in 1.6% and warfarin in 1.4%. 	The results were highly sensitive to the patient population under consideration. Rivaroxaban and dabigatran 110 mg were unlikely to be cost-effective. In different scenarios, apixaban or dabigatran 150 mg were optimal. Thus, the choice between these options may come down to the price of apixaban and further evidence on the impact of major and minor bleeds with dabigatran.
[32]	US	Dabigatran, rivaroxaban and apixaban vs. warfarin	Societal	30 years	CUA Markov model	Riva: USD 3,190/QALY Dabi: USD 11,150/QALY Apixa: USD 15,026/QALY	<ul style="list-style-type: none"> • Probabilities contributing the most leverage to model results were age-associated probabilities of ischemic stroke, ICH and MI. • In a Monte Carlo probabilistic sensitivity analysis, apixaban, dabigatran, rivaroxaban and warfarin were cost-effective in 45.1%, 40%, 14.9% and 0% of the simulations, respectively. 	The NOACs evaluated in this study were more cost-effective compared with warfarin treatment for stroke prevention in patients with NVAf. Of the 3 NOACs, apixaban 5 mg was the preferred anticoagulant for this population because it was most likely to be the cost-effective treatment option at all WTP thresholds >USD 40,000/QALY.

[33]	US	Apixaban vs. warfarin	Payer	Lifetime	CUA Markov model	Apixaban was dominant	<ul style="list-style-type: none"> • The base-case results were sensitive to variability in the drug cost of apixaban, treatment costs of warfarin, bi-weekly cost of ICH, the baseline rate of ICH, the relative efficacy of ICH on apixaban compared to warfarin and time horizon. • Two-way sensitivity analyses of various baseline risks of stroke and ICH demonstrated apixaban is cost-effective when stroke and ICH were varied jointly across plausible ranges. • Monte Carlo simulation: apixaban was a dominant strategy in 57% of the simulations and cost-effective in 98%. 	Apixaban is likely at minimum cost-effectiveness in AF patients with at least one additional risk factor for stroke and a baseline ICH risk of about 0.8%. These results are sensitive to several model assumptions; particularly those related to ICH.
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[34]	US	Apixaban vs. warfarin	Societal	20 years	CUA Markov model	USD 11,400/QALY	<ul style="list-style-type: none"> • Variables with the greatest influence on our results were the monthly cost of recurrent stroke or combined stroke and ICH, the starting age of the cohort, the relative risk of ischemic stroke with apixaban vs. warfarin and the cost of apixaban. • Apixaban was cost-effective in 62% of Monte Carlo simulations. 	Based on the available data, apixaban appears to be a cost-effective alternative to VKAs for secondary stroke prevention in patients with AF.
[35]	US	Apixaban vs. aspirin	Payer	1 year and 10 years or death	CUA Markov model	1 year: Apixaban resulted in an inferior strategy (more costly but no more effective). 10 years: Apixaban was dominant.	<ul style="list-style-type: none"> • In 1-way sensitivity analyses the results were most sensitive to changes in the model's time horizon, the baseline rate of stroke on aspirin based on CHADS2 score, the monthly cost of major stroke and the effect of apixaban on ischemic stroke. • Probabilistic sensitivity analyses suggested apixaban would only be a cost-effective alternative to aspirin 11% of the time in the 1-year model, but cost-effective or dominant 96.7% and 87.5% of iterations in the 10-year model. 	Our trial-length model found apixaban to be more costly and less effective than aspirin; however, as the time horizon was extended, apixaban became cost-effective and eventually economically dominant.

AF: atrial fibrillation; Apixa: apixaban; CE: cost-effectiveness; CEA: cost-effectiveness analysis; CEAC: cost-effectiveness acceptability curve; CUA: cost-utility analysis; CV: cardiovascular; Dabi: dabigatran; Edoxa: edoxaban; ICER: incremental cost-effectiveness ratio; ICH: International Council for Harmonisation; IS: ischemic stroke; LYG: life years gained; MI: myocardial infarction; NHS: National Health Service; NOAC: new oral anticoagulant; NVAF: non-valvular atrial fibrillation; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life years; Riva: rivaroxaban; RR: relative risk; SA: sensitivity analysis; TTR: time in therapeutic range; VKA: vitamin K antagonists; War: warfarin; WTP: willingness to pay;