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Health Technology Assessment (HTA)

HTA Report

Title	Oral anticoagulants for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation
Authors	Thomas Vreugdenburg, Konstance Nicolopoulos, Magdalena Ruth Moshi, Danielle Stringer, Alun Cameron Royal Australasian College of Surgeons
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Bundesamt für Gesundheit
Sektion Health Technology Assessment
Schwarzenburgstrasse 157
CH-3003 Bern
Schweiz
Tel.: +41 58 462 92 30
E-mail: hta@bag.admin.ch

Executive Summary

Objective

The aim of this health technology assessment (HTA) report is to evaluate the efficacy, effectiveness, safety, cost-effectiveness and budget impact of direct oral anticoagulants (DOACs) compared to vitamin K antagonists (VKA) in patients with nonvalvular atrial fibrillation (NVAF). In addition, ethical, legal, social and organisational issues related to DOAC and VKA use are explored.

Methods

Systematic searches were conducted in 4 databases (PubMed, Embase, Cochrane Library, INAHTA) up to 29 March 2022. In addition, grey literature sources and ongoing clinical trials up to 29 August 2022 were retrieved. Publications were limited to English, German, French and Italian.

Systematic reviews, randomised controlled trials (RCTs) and non-randomised studies of interventions (NRSI) were included that investigated the use of a DOAC currently reimbursed in Switzerland (i.e. apixaban, dabigatran, edoxaban, rivaroxaban), compared to a VKA currently reimbursed in Switzerland (i.e. phenprocoumon, acenocoumarol) or warfarin in patients with NVAF. Warfarin is not used in Swiss practice but is considered to be equivalent to other VKAs; therefore, studies that used warfarin as the main comparator were only included in the absence of evidence for acenocoumarol or phenprocoumon. Outcomes included all-cause mortality; bleeding, including major/life-threatening, gastrointestinal (GI), intracranial and clinically-relevant; stroke or systemic embolism (SE), including ischaemic and haemorrhagic stroke; health-related quality of life; adherence to treatment plan; persistence with therapy; and discontinuations due to adverse events.

Risk of bias was evaluated using AMSTAR-II (systematic reviews), Cochrane RoB 2.0 tool (RCTs), ROBINS-I tool (NRSIs). GRADE was used to determine the overall strength of evidence for selected outcomes.

Separate pairwise meta-analyses were conducted at longest follow-up (range 3–30 months) for RCTs and NRSIs, per outcome. Meta-analyses were conducted using random effects inverse-variance models. Heterogeneity was evaluated visually and quantitatively (i.e. I^2, Chi^2, Tau^2 and I^2).

A Markov model was developed to evaluate the cost-effectiveness of apixaban, dabigatran, edoxaban and rivaroxaban relative to VKAs. Four pairwise analyses—from the perspective of the Swiss healthcare payer—were conducted. The robustness of the economic findings was explored via deterministic and probabilistic sensitivity analysis. In addition, expected payer costs for OAC therapies in patients with atrial fibrillation (AF), under current policy and practice conditions, were

extrapolated over the period 2022 to 2026. The financial implications of potential policy changes were not considered given the clinical and economic findings favoured the use of DOACs.

Clinical results

Randomised controlled trials

In total, 9 RCTs were included (n=74,472), all of which compared DOAC to warfarin: 2 evaluated warfarin compared to apixaban (n=18,423), 2 compared it to dabigatran (n=18,283), 3 compared it to edoxaban (n=22,224) and 2 compared it to rivaroxaban (n=15,542). Of the included RCTs, 3 were considered to have a low risk of bias and 6 a high risk of bias.

All-cause mortality slightly favoured DOACs, reaching statistical significance for edoxaban at 30 mg once daily (7 fewer deaths per 1,000 patients [from 13 fewer to 0 fewer], moderate certainty evidence). Compared to warfarin, there was a reduction in reported events of major/life-threatening bleeding for a number of DOACs (apixaban 5 mg twice daily, dabigatran 110 mg twice daily, edoxaban 30 mg and edoxaban 60 mg), with an estimated effect size of 3 to 20 fewer events per 1,000 patients. All DOACs showed a statistically significant reduction in the rate of intracranial bleeding compared to warfarin, with the effect size ranging from 6 to 13 fewer events per 1,000 patients. The impact of DOACs on GI bleeding varied—edoxaban 30 mg showed statistically significant reductions compared to warfarin. Dabigatran 150 mg, rivaroxaban 20 mg and edoxaban 60 mg showed a statistically significant increase in GI bleeding. There was no statistically significant difference with apixaban. Edoxaban (30 and 60 mg) significantly reduced the number of clinically-relevant bleeding events (58 fewer per 1,000, from 68 fewer to 48 fewer; and 25 fewer per 1,000, from 37 fewer to 14 fewer, respectively). All other DOACs, where reported, showed no significant difference compared to warfarin. Across all DOACs (type and dose) there was no difference in total stroke and SE compared to warfarin.

Non-randomised controlled trials

In total, 10 NRSIs were included that compared DOACs to either phenprocoumon, acenocoumarol or an unspecified VKA from a country that primarily uses one of these 2 drugs (n=1,772,002). Of these, 8 NRSIs evaluated apixaban (n=183,780), 9 evaluated dabigatran (n=144,742), 2 evaluated edoxaban (n=16,531) and 7 evaluated rivaroxaban (n=417,689). All studies were at a high or critical risk of bias, primarily due to unmeasured confounding and significant, unbalanced dropouts between treatment groups. The NRSI results were difficult to interpret due to the risk of bias and conflicting results depending on the choice of outcome measure (i.e. hazard ratio [HR] or risk ratio [RR]).

Economic results

Under base-case assumptions, all DOACs were found to be cost-saving compared to VKAs while improving patient outcomes (quality-adjusted life years lived). All DOACs increased drug costs relative to VKAs but were cost-saving in terms of monitoring and clinical event costs. Sensitivity analyses found the dominance of each DOAC to be robust. The relative efficacy of each DOAC with respect to all-cause mortality was the key model driver in all 4 comparisons. The high monitoring costs associated with VKAs proved influential; removing this reverted the dominance of all 4 DOACs.

Use of relative effect estimates from NRSIs, rather than RCTs, impacted the economic outcomes. Nevertheless, the conclusions regarding the cost-effectiveness of DOACs were drawn based on the RCT-based analyses alone because the NRSI evidence itself was conflicting and difficult to interpret.

Under current policy conditions, OACs for patients with AF were estimated to be responsible for a cost of CHF128.0 million in 2021, increasing to an anticipated cost of CHF188.2 million in 2026. Expected monitoring costs were projected to decline; however, overall treatment costs (i.e. drug and monitoring costs combined) were projected to rise to an anticipated CHF233.0 million in 2026.

Ethical, legal, social and organisational issues

A total of 21 studies relevant to the ELSO domains were identified from systematic and targeted, non-systematic keyword searches. No legal issues were identified. Social issues associated with DOAC include patient-related, physician-related and healthcare system-related factors that affect adherence. An ethical issue around DOAC use relates to their benefit/harm profile. Although a favourable benefit/harm profile of DOACs was demonstrated from the RCT evidence, the NRSI data was difficult to interpret. In relation to the main organisational impacts on practice, DOACs have fewer monitoring requirements compared to VKAs, which require international normalised ratio (INR) testing approximately every 20 days.

Conclusions

The RCT evidence demonstrated favourable outcomes for the use of DOACs, noting that the evidence had a mixed risk of bias (ranging from low to very high). The NRSI evidence was difficult to interpret due to unmeasured confounding, significant unbalanced dropouts between treatment groups, and conflicting results depending on the choice of outcome measure (i.e. HR or RR). As such, the RCT evidence was deemed to provide more reliable results and was used as the basis for the economic evaluation. The economic evaluation supports the cost-effectiveness of DOACs. This finding is driven primarily by small improvements in all-cause mortality and high costs associated with INR monitoring for VKAs. Overall, payer costs for OAC use in AF are expected to increase due to (anticipated) continued growth in the relative use of DOACs and expected demographic changes.

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Abbreviations and acronyms

95% CI	95% confidence interval
AF	Atrial fibrillation
CHA2DS2-VASc	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/transient ischaemic attack, Vascular disease, Age 65–74 years, Sex category (female)
CrCl	Creatinine clearance
CUA	Cost–utility analysis
CYP	Cytochrome
DIC	Deviance information criterion
DOAC	Direct oral anticoagulant
FOPH	Federal Office of Public Health
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly (>65 years), Drugs/alcohol concomitantly
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial haemorrhage
IHE	Institute of Health Economics
INAHTA	International Network of Agencies for Health Technology Assessment
INR	International normalised ratio
IS	Ischaemic stroke
MCMC	Markov chain Monte Carlo
N.A.	not applicable
NICE	National Institute for Health and Care Excellence (NICE)
NMA	Network meta-analysis
NOAC	Novel oral anticoagulant

NRSI	Non-randomised studies of interventions
NVAF	Non-valvular atrial fibrillation
OKP	Obligatorische Krankenpflegeversicherung (mandatory health insurance)
PICO	Population, intervention, comparator, outcome
PICO (EO)	population, intervention, comparator, outcome, (economic outcomes)
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RoB 2.0	Cochrane Risk of Bias 2.0
ROBINS-I	Cochrane Risk of Bias in Non-randomised Studies – of Interventions
SD	Standard deviation
SE	Systemic embolism
TSOAC	Target-specific oral anticoagulant
UK	United Kingdom
VKA	Vitamin K antagonist
WHO	World Health Organization

Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology, their execution and the results are described. The analytical process is comparative, systematic, and transparent and involves multiple stakeholders. The domains covered in an HTA report include clinical effectiveness and safety, costs, cost-effectiveness and budget impact, and ethical, legal, social and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1 Policy question and context

Each HTA topic entails a policy and a research question. The ***policy question*** is a request to regulate a reimbursement policy and is aimed at securing financing of health technologies. Such a request, related to a particular health technology, typically addresses an existing controversy around a technology.

In Switzerland, both vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) are currently covered by mandatory health insurance (OKP) for the prevention of stroke and systemic embolism (SE) in patients with non-valvular atrial fibrillation (NVAF).[1] For many years VKAs were the predominant option in stroke prophylaxis for patients with NVAF. With the introduction of DOACs more than 10 years ago, the use of VKAs has gradually decreased, while the use of DOACs increased.[2] However, the estimated daily cost of DOACs is considerably higher than for VKAs. In addition, evidence from a 2018 observational study from Germany indicated patients with NVAF that were treated with DOACs reported a significantly higher likelihood of:

- death (HR 1.22, 95% CI 1.17 to 1.28; 11.3 vs 9.2 events per 100 patient years)
- ischaemic stroke (HR 1.92, 95% CI 1.69 to 2.19; 2.18 vs 1.15 events per 100 patient years)
- non-specified stroke (HR 1.93, 95% CI 1.13 to 3.32; 0.11 vs 0.05 events per 100 patient years)
- myocardial infarction (HR 1.31, 95% CI 1.13 to 1.25; 1.33 vs 1.06 events per 100 patient years)
- transient ischaemic attack (HR 1.44, 95% CI 1.21 to 1.70; 0.99 vs 0.65 events per 100 patient years)
- arterial embolism (HR 1.81, 95% CI 1.36 to 2.34; 0.39 vs 0.22 events per 100 patient years)
- severe bleeding (HR 1.95, 95% CI 1.74 to 2.20; 2.47 vs 1.29 events per 100 patient years).[3]

This evidence prompted a submission to the Federal Office of Public Health (FOPH) by an external applicant to re-evaluate the use of DOACs for NVAF in the Swiss population. The policy question informing this HTA topic is thereby a request to restrict or further regulate the reimbursement policy for DOACs in Switzerland.

2 Research question

To answer a policy question, the research question must be defined and answered first. The ***research question*** is an answerable inquiry into the HTA topic, which requires data collection and analysis. Research questions are specific and narrow. This HTA report will assess the following research question:

What are the clinical, economic, legal, social, ethical and organisational benefits and harms of DOACs compared to VKAs for the prevention of stroke and other thromboembolic events in patients diagnosed with NVAF?

3 Medical background

Atrial fibrillation (AF), the most common form of cardiac arrhythmia, is defined by the European Society of Cardiology (ESC) as 'a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction'.[4] Abnormal electrical signals in the atria cause them to beat irregularly and out of sync with the ventricles, decreasing the heart's ability to pump blood through the body and weakening the heart muscle over time, potentially leading to dysfunction and heart failure. AF has 3 typical patterns of presentation: paroxysmal (spontaneously resolves within 7 days, with or without treatment); persistent (lasts more than 7 days and requires treatment); and longstanding or chronic (lasts more than 12 months and is resistant to treatment). AF is considered permanent when it is refractory to all available treatments.[4,5]

Any condition that causes inflammation, damage or ischaemia of the heart muscle can predispose individuals to developing AF. However, the most common causes of AF are advanced age, chronic heart failure, coronary heart disease, underlying heart and lung disease, increased alcohol consumption, obesity, hypertension and endocrine disorders.[4-6] Most cases of AF are related to underlying cardiovascular disease.[4-6] The term valvular AF is generally used to differentiate patients with AF who have moderate or severe mitral stenosis or a mechanical prosthetic heart valve(s) (i.e. conditions that substantially increase thromboembolic risk), from other patients who are considered to have NVAF. However, since NVAF does not imply the absence of valvular heart disease this terminology has been recently deemed confusing and outdated.[4,7] Nonetheless, given the ubiquity of these definitions in the published literature on DOACs (up to 20% of patients enrolled in DOAC trials had various valvular defects, including mild mitral stenosis[8]), the term NVAF will be used in this report.

3.1 Symptoms and prognosis

The turbulent blood flow resulting from AF can cause clots to form within the heart, most commonly in the left atrial appendage. If these clots dislodge, they can travel to the brain or other organs, resulting in stroke or SE, respectively.[5] Patients with AF may be asymptomatic, or they may experience symptoms such as chest pain, palpitations, fast heart rate, shortness of breath, nausea, dizziness, severe sweating and fatigue.[5,9]

AF is associated with an increased risk of stroke (5-fold) and heart failure and death (2-fold) compared with the general population.[4-6] Approximately 20% of patients with a first-time stroke have concomitant AF, and AF-related strokes are associated with a 50% increased risk of disability and a 60% increased risk of death at 3 months, compared with strokes of other aetiologies.[10,11] AF is associated with a 1.9% risk of stroke per year, which can rise as high as 17% per year when other risk factors are present, such as diabetes, hypertension, advanced age, heart failure, peripheral vascular disease and previous stroke or ischaemic cardiac event.[12] The number of strokes caused by AF-related thromboembolisms may be even higher than currently thought because the cause of approximately 30% of ischaemic strokes (IS) is unclear, and up to one-third of these patients may have AF.[13] Therefore, anticoagulation is an important prophylactic strategy for patients with NVAF who have an intermediate or high risk of stroke.

3.2 Epidemiology and burden of disease

In Europe, 1–4% of the population have AF, corresponding to an incidence of 0.2 to 0.4 per 1,000 person-years.[4,6] Given the increasing longevity of the population, the frequency of AF is expected to rise 2- to 3-fold, such that by 2060 nearly 18 million people in Europe will be affected by AF.[4,6,14,15] The prevalence of AF is higher among men than women (ratio of 1.2:1) and is strongly correlated with increasing age. AF is present in approximately 4% of those age 60–70 years and in 10–17% of those age 80 years or older.[4,6]

Permanent AF generally accounts for 50% of cases, whereas paroxysmal and persistent AF each account for 25% of cases, noting that AF follows a continuous evolution from paroxysmal to persistent.[6] The Basel AF cohort study (BEAT-AF) reported that among participants with recent onset AF, 62% had paroxysmal AF and 38% had non-paroxysmal AF (30% had persistent and 8% had permanent AF).[16]

AF is often present with other illnesses, most commonly hypertensive heart disease (22–36%), coronary heart disease (14–32%), valvular heart disease (12–26%) and cardiomyopathy (6–10%).[17,18] Consequently, patients with AF have a significantly lower quality of life than the general population, as well as an increased relative risk of heart failure (399%), cardiovascular mortality (103%), major cardiovascular events (96%), ischaemic heart disease (61%), chronic kidney disease (64%), dementia or cognitive impairment (40%) and peripheral artery disease (31%).[17,18]

Between 10% and 40% of patients with AF are hospitalised annually due to heart failure, arrhythmia recurrence, stroke and bleeding events.[19] A German registry study conducted between 2009 and 2012 reported 18.5% of patients followed for one year after enrolment were hospitalised, noting that 15.1% of hospital admissions were related to needing AF treatment (e.g. electrical conversion, ICD implantation, catheter ablation, and drug conversion).[20] Hospitalisations account for 50–70% of the total costs of caring for patients with AF.[21] In addition, some form of caregiver assistance is required in 63% of elderly

patients with AF and in 80% of patients recovering from AF-related stroke.[22] In Europe, AF-related stroke costs approximately 7–60% more than non-AF-related stroke due to the longer hospital stays, need for inpatient rehabilitation and higher likelihood of stroke recurrence.[23,24] Overall, the estimated annual cost of AF to healthcare systems in Europe range from EUR660–3,286 million, absorbing up to 2.6% of total annual healthcare expenditures.[24]

4 Technology

Clot formation to control bleeding from a damaged blood vessel involves multiple interlinked steps within the following 3 broadly defined stages: initiation (disturbance of the vascular endothelium and clotting factors); activation of various proenzymes to produce thrombin; and fibrin clot formation.[25-28] There are 2 main pathways in the clotting cascade: the intrinsic pathway and the extrinsic pathway. External trauma activates the extrinsic pathway and involves factor VII.[28] Trauma inside the vascular system activates the intrinsic pathway, which involves factors VIII, IX, XI and XII. Both pathways share a common ending where factor X is activated (factor Xa), which then converts prothrombin (factor II) to large amounts of thrombin (factor IIa).[26,28] In the final stage of the coagulation cascade, thrombin cleaves fibrinogen into fibrin monomers and activates factor XIII (factor XIIIa), which cross-links the fibrin monomers to form a stable blood clot.[25-28]

4.1 Anticoagulants

Anticoagulation medications are directed at various sites of the coagulation pathway to prevent clot formation. Long-term oral anticoagulation is the recommended first-line therapy for preventing primary and secondary stroke in patients with AF, particularly in those with a moderate to high risk of thromboembolic events.[4,8,29] Since oral anticoagulants (OAC) increase the potential for bleeding, the benefits and harms of prescribing this medication must be considered for each patient. The CHA_2DS_2-VASc[A] score[30] is used to assess embolic risk in patients with AF, with OAC being recommended (i.e. Class IA = strong recommendation based on data sourced from RCTs or meta-analyses) when patients have NVAF and a CHA_2DS_2-VASc score ≥2 (men) or ≥3 (women). OAC is considered (i.e. Class IIa = conflicting evidence; weight of evidence in favour of efficacy) for a score of 1 (men) or 2 (women)

[A] **CHA_2DS_2-VASc: C**ongestive heart failure, **H**ypertension, **A**ge ≥75 years, **D**iabetes mellitus, previous **S**troke/transient ischaemic attack, **V**ascular disease, **A**ge 65–74 years, **S**ex **c**ategory (female).

(maximum score of 9).[4] The HAS-BLED[B] score[31] is used to address modifiable bleeding risk factors and to identify patients at high risk of bleeding (score ≥3) who may need more frequent clinical review when receiving anticoagulant medication.[4] Anticoagulant treatment is usually managed by a family physician or specialised anticoagulation clinic,[32] noting that adequate medical counselling and adherence to treatment plans are necessary for stable disease management.[33,34]

4.1.1 Vitamin K Antagonists (VKA)

VKAs have been the mainstay of long-term stroke prevention in patients with NVAF for over half a century.[13,35] The most used VKAs (4-hydroxycoumarins) are derived from a class of phytochemicals called coumarins. These drugs, which include warfarin, phenprocoumon and acenocoumarol, have similar chemical structures and mechanisms of action. VKAs do not directly antagonise the action of vitamin K but rather act indirectly through inhibition of the enzyme vitamin K epoxide reductase, which converts inactive vitamin K to its active form. VKAs deplete functional vitamin K reserves, effectively inhibiting the formation of the vitamin K-dependent clotting factors II, VII, IX, X and the anticoagulant proteins S and C.[13,25,32]

Warfarin, phenprocoumon and acenocoumarol are metabolised in the liver by various hydroxylation reactions catalysed by cytochrome P450 (CYP) enzymes. However, each drug is metabolised by a different combination of CYP enzymes, resulting in their differing half-lives (***Table 1***).

4.1.2 Direct oral anticoagulants

The terms DOAC, new or novel oral anticoagulants (NOACs) and target-specific oral anticoagulants (TSOACs) refer to OACs that inhibit clotting factors IIa (thrombin) or Xa. DOAC is the term preferred by the International Society of Thrombosis and Haemostasis.[25,36] Unlike VKAs which act indirectly through inhibition of vitamin K formation, DOACs act directly on clotting factors to stop the formation of a fibrin clot.

Direct factor IIa inhibitors (thrombin) inhibit the cleavage of fibrinogen to fibrin by thrombin and include intravenous drugs for heparin-induced thrombocytopenia (e.g. bivalirudin, argatroban) and the oral drug dabigatran, which is used for patients with NVAF.[25] **Direct factor Xa inhibitors,** which include rivaroxaban, apixaban, edoxaban and betrixaban, bind directly to factor Xa to inhibit the cleavage of prothrombin to thrombin.[25,28]

The advent of DOACs in the last decade has provided new options for anticoagulation. International guidelines now recommend DOACs over VKAs as first-line therapy for stroke prevention in most patients

[B] **HAS-BLED: H**ypertension, **A**bnormal renal/liver function, **S**troke, **Bl**eeding history or predisposition, **L**abile international normalised ratio, **E**lderly (>65 years), **D**rugs/alcohol concomitantly.

with NVAF.[4,8,29] Four DOACs are approved in Switzerland: rivaroxaban (Xarelto®), edoxaban (Lixiana®), apixaban (Eliquis®) and dabigatran (Pradaxa®) (***Table 1***). Although DOACs are usually referred to as a uniform pharmacological class, pharmacokinetic properties differ among them and there is a growing evidence from indirect comparisons and observational studies suggesting that each DOAC may have a specific risk profile.[37]

4.2 Anticoagulant utilisation in Switzerland

In Switzerland, VKAs and DOACs are prescribed for the prevention of stroke and SE in patients with NVAF. The total costs of DOACs rose from CHF60 million in 2014 to CHF219 million in 2020, while the total costs of VKAs decreased from CHF6 million in 2014 to CHF3 million in 2020 (Tarifpool: © SASIS AG – Datenaufbereitung: © COGE).

Although 60% of strokes secondary to AF can be avoided with the use of anticoagulants, there is still an appreciable annual residual stroke risk of approximately 1.7% for VKAs and 1.4% for DOACs.[38,39] The increasing utilisation and rising costs of DOACs in Switzerland, in tandem with a recent observational study questioning their efficacy and safety in comparison to VKAs, has prompted a closer evaluation of the efficacy, effectiveness, safety and costs of these medications in patients with NVAF.

Table 1 Characteristics of commonly prescribed oral VKAs and DOACs in patients with NVAF

Drug (brand name)/ Manufacturer	Recommended Dose	Half-life	Metabolism	Routine Monitoring	Contraindications
Vitamin K Antagonists					
Warfarin [a]	1.5–12 mg once daily	36–42 hours	Renal 92%	Yes	Drug hypersensitivity, non-adherence to medication and blood monitoring, uncontrolled hypertension, pregnancy, all pathological situations where the risk of haemorrhage outweighs the possible clinical benefit (e.g. severe liver disease, renal failure, gastrointestinal ulcer, active bleeding, acute bacterial endocarditis, pericardial effusion, recent surgery and planned procedures involving the nervous system, spine or eye)
Phenprocoumon (Marcoumar®) [b] MEDA Pharma GmbH	1.5–4.5 mg once daily	5–6 days	Renal 65% Biliary/intestinal 35%	Yes	
Acenocoumarol (Sintrom®) [b] Medius AG	1–8 mg once daily	8–11 hours	Renal 65% Biliary/intestinal 35%	Yes	
Factor Xa Inhibitors					
Apixaban (Eliquis®) [b] Bristol-Myers Squibb SA	2.5–5 mg twice daily	8–12 hours	Renal 27% Hepatic 73%	No	CrCl <15 ml/minute, active bleeding, liver disease associated with coagulopathy and clinically significant risk of bleeding or severe liver failure (Child-Pugh class C), mechanical heart valves or moderate to severe mitral stenosis (not studied), antiphospholipid syndrome, drug hypersensitivity
Edoxaban (Lixiana®) [b] Daiichi Sankyo (Schweiz) AG	15–-60 mg once daily	10–14 hours	Renal 50% Biliary/intestinal 50%	No	CrCl <15 ml/minute, active bleeding, liver disease associated with coagulopathy and clinically significant risk of bleeding, mechanical heart valves or moderate to severe mitral stenosis (not studied), antiphospholipid syndrome, drug hypersensitivity, concomitant use of other anticoagulants, pregnancy and lactation
Rivaroxaban (Xarelto®) [b] Bayer (Schweiz) AG	15–20 mg once daily	7–8 hours	Renal 50%, hepatic Eliminated non-metabolised 33%	No	CrCl <15 ml/minute, active bleeding, acute gastrointestinal ulcer or ulcerative gastrointestinal disease, severe liver disease or liver disease associated with coagulopathy and clinically significant risk of bleeding, acute endocarditis of bacterial origin, mechanical heart valves or moderate to severe mitral stenosis (not studied), antiphospholipid syndrome, drug hypersensitivity, pregnancy and lactation
Factor IIa Inhibitors (thrombin)					
Dabigatran (Pradaxa®) [b] Boehringer Ingelheim (Schweiz) GmbH	110–150 mg twice daily	12–18 hours	Renal 80%	No	CrCl <30 ml/minute, active bleeding, organ damage with risk of clinically significant bleeding, severe liver disease or liver failure, mechanical heart valves or moderate to severe mitral stenosis (not studied), antiphospholipid syndrome, concomitant use of P-glycoprotein inhibitors, drug hypersensitivity

Abbreviations: CrCl: creatinine clearance; **DOAC**: direct oral anticoagulant; **NVAF**: non-valvular atrial fibrillation; **VKA**: vitamin K antagonist.

Notes: [a] Warfarin is not approved for use in Switzerland. [b] In Switzerland these drugs are approved for other indications in addition to NVAF.

Sources: Black et al 2019,[27] Hindricks et al 2021,[4] Raschi et al 2019,[37] Ray & Keyrouz 2014,[40] Steffel et al 2021,[29] Swissmedic 2021,[41] Ufer 2005,[42] Spezialitätenliste,[1] Swissmedic.[41]

5 Population, Intervention, Comparator, Outcome (PICO)

Table 2 PICO criteria

Population	Patients with NVAF (AF in the absence of moderate/severe mitral stenosis or a mechanical prosthetic heart valve) who are eligible for OAC
Intervention(s)	**Direct-acting oral anticoagulant (DOAC)** 1. Dabigatran (Pradaxa®) – 110 mg or 150 mg twice daily 2. Apixaban (Eliquis®) – 2.5 mg or 5 mg twice daily 3. Edoxaban (Lixiana®) – 30 mg or 60 mg once daily 4. Rivaroxaban (Xarelto®) – 15 mg or 20 mg once daily
Comparator(s)	**Vitamin K antagonists (VKA)** 1. Acenocoumarol (Sintrom®) – 1–8 mg once daily 2. Phenprocoumon (Marcoumar®) – 1.5–4.5 mg once daily 3. Warfarin – 1.5–12 mg once daily [a]
Outcome(s)	**Clinical outcomes** **1. All-cause mortality** 2. Cardiovascular-related mortality 3. Bleeding: a. Major/life-threatening bleeding b. Intracranial bleeding c. Gastrointestinal bleeding d. Clinically-relevant bleeding 4. Stroke or systemic embolic event **5. Stroke:** a. Ischaemic stroke b. Haemorrhagic stroke 6. Cognitive functioning 7. Adherence: the extent to which the patient conforms to the agreed behaviours, with respect to timing dosage and frequency of medication-taking.[43] 8. Persistence: the duration of time from initiation to discontinuation of therapy.[43] [b] **9. Health-related quality of life** 10. Treatment discontinuation due to adverse events **Health economic outcomes** 1. Direct medical technology costs of the technology and related events (resource use valuation) 2. Cost-effectiveness/cost-utility 3. Budget-impact

Abbreviations:

AF: atrial fibrillation; **NVAF**: non-valvular atrial fibrillation.

Notes:

[a] Studies on warfarin were only considered for inclusion when there was no evidence for phenprocoumon or acenocoumarol.

[b] Persistence can be reported as both a continuous or dichotomous variable. The continuous variable is defined as the length of time between treatment initiation and treatment discontinuation. The dichotomous variable is defined as the number of patients that complete the treatment within the pre-defined time period.[43]

5.1 Population

The population of interest—patients with NVAF—reflects current restrictions on the use of DOACs in Switzerland for patients with AF (per the indications approved by Swissmedic).[41] The term NVAF is generally used to differentiate patients who do not have moderate/severe mitral stenosis or a mechanical prosthetic heart valve(s) from other patients who are considered to have valvular AF. However, it should be noted that NVAF does not imply the absence of valvular heart disease.[4,7] This differentiation is appropriate given that it has been used as an exclusion criterion in pivotal DOAC trials.[44]

5.2 Intervention

Oral preparations of the following 4 DOACs approved in Switzerland for NVAF were eligible for inclusion: apixaban 2.5 or 5 mg twice daily, dabigatran 110 mg or 150 mg twice daily, edoxaban 30 mg or 60 mg once daily, rivaroxaban 15 mg or 20 mg once daily. While the 3 direct factor Xa inhibitors (apixaban, edoxaban and rivaroxaban) share a similar mechanism of action, each drug was assessed individually, rather than as a class, against the comparator. The direct factor Xa inhibitor betrixaban was not included because it is not approved for NVAF in Switzerland. The direct thrombin inhibitor, which targets a different point in the coagulation cascade, was assessed separately. A specific inclusion criterion based on dose regimen was not specified, since dosing can vary depending on patient factors such as age, degree of renal impairment and concomitant medication use.

5.3 Comparator

The relevant comparators are oral preparations of acenocoumarol and phenprocoumon, which are approved in Switzerland for patients with NVAF. However, a scoping search did not identify any randomised controlled trial (RCT) evidence specifically on acenocoumarol or phenprocoumon. In the absence of evidence for acenocoumarol or phenprocoumon, warfarin was included as a substantially equivalent comparator drug. Although warfarin is not approved in Switzerland for NVAF, it is the most widely prescribed and well-studied of the coumarin derivatives and has a large RCT evidence base. Since warfarin, acenocoumarol and phenprocoumon belong to the same class of drugs and are substantially equivalent in terms of their chemical structure and mechanism of action, VKAs were grouped as a class comparator for the RCT evidence, including warfarin. For the non-randomised studies of interventions (NRSI), only acenocoumarol and phenprocoumon were included, because there is evidence available for these drugs. This strategy avoided the large evidence gap that would be present among studies of higher levels of evidence if only acenocoumarol and phenprocoumon were used as comparators. Trials of VKAs that reported a target international normalised ratio (INR) <2 or >3 were excluded.[4]

5.4 Outcomes

The critical outcomes related to anticoagulant therapy for NVAF relate to bleeding events (i.e. safety outcomes) and embolic events related to inadequately treated NVAF (i.e. effectiveness outcomes).[19,45,46] The list of outcomes provided in the PICO criteria (***Table 2***) were informed by a panel of clinical and methodological experts, as well as guidance from the International Consortium for Health Outcomes Measurement, the European Medicines Agency and ESC on relevant outcome measures for patients with AF.[19,45,46] In order to keep the scope of the HTA report targeted on the most relevant outcomes, only the most important patient-relevant outcomes have been included.

6 HTA key questions

For the evaluation of the technology the following key questions covering the central HTA domains are addressed:

1. Are DOACs efficacious/effective compared to VKAs for the prevention of stroke and other thromboembolic events in patients with NVAF who are eligible for OAC?
2. Are DOACs safe compared to VKAs for the prevention of stroke and other thromboembolic events in patients with NVAF who are eligible for OAC?
3. Are there any adherence issues with DOACs compared to VKAs?
4. What are the costs associated with DOACs compared to VKAs?
5. How cost-effective are DOACs compared to VKAs?
6. What is the budget impact of DOACs compared to VKAs?
7. Are there any legal, social, ethical or organisational issues associated with the use of DOACs and VKAs?

7 Effectiveness, efficacy and safety

Summary statement efficacy, effectiveness and safety

RCT findings: 9 RCTs were included, all of which compared a DOAC to warfarin. The reported risk of outcomes per 1,000 are reported at longest follow-up (range 3-30 months). All-cause mortality slightly favoured DOACs compared to warfarin, reaching statistical significance and with high certainty for edoxaban 30 mg once daily. Compared to Warfarin, there was a reduction in reported events of major/life-threatening bleeding across a number of DOACs (apixaban 5 mg, dabigatran 110 mg, edoxaban 30 mg and edoxaban 60 mg), with an estimated effect size of 3 to 20 fewer events per 1,000 patients. All DOACs showed a statistically significant reduction in the rate of intracranial bleeding when compared to warfarin, with the effect size ranging from 6 to 13 fewer events per 1,000 patients. The impact of DOACs on gastrointestinal bleeding (GI) varied; edoxaban 30 mg showed statistically significant reductions compared to warfarin. Dabigatran 150 mg, rivaroxaban 20 mg and edoxaban 60 mg showed statistically significant increases in GI bleeding. Apixaban showed no statistically significant difference. Edoxaban (30 mg and 60 mg) significantly reduced the number of clinically-relevant non-major/life-threatening bleeding events (58 and 25 fewer per 1,000, respectively). All other DOACs, where reported, showed no significant differences compared to warfarin. Across all DOACs (type and dose) there was no difference in all stroke and SE compared to warfarin.

NRSI findings: 10 NRSIs were included that compared DOACs to either phenprocoumon or acenocoumarol. All-cause mortality results were challenging to interpret. Studies that reported hazard ratios (HR) reported statistically significant increases in all-cause mortality for edoxaban and rivaroxaban, but no difference compared to apixaban or dabigatran. In contrast, studies that reported risk ratios (RR) reported significant reductions favouring dabigatran. These conflicting results are not easily explained. There were statistically significant reductions in major/life-threatening bleeding in favour of apixaban and dabigatran, regardless of which outcome measure was used. In contrast, there was a significant difference with an increase in major/life-threatening bleeding for rivaroxaban, regardless of outcome measure. Intracranial bleeding was statistically significantly reduced for apixaban and rivaroxaban in both the HR and RR analyses. The results for dabigatran were conflicting (HR analysis in favour of dabigatran, RR results reported no difference). GI bleeding was statistically significantly reduced for apixaban in both the HR and RR analyses; however, the results for dabigatran and rivaroxaban were conflicting between the HR and RR analyses. Clinically-relevant bleeding was statistically significantly reduced for apixaban and dabigatran; there was no difference for edoxaban; and it was statistically significantly increased for rivaroxaban. Stroke and SE results were challenging to

interpret. Across all DOACs HR reported no difference in total stroke and SE compared to phenprocoumon or acenocoumarol. However, the RR reported SE statistically significantly reduced stroke for dabigatran and rivaroxaban.

7.1 Methodology: effectiveness, efficacy and safety

The methods were developed following the Cochrane Handbook for Systematic Reviews of Interventions,[47] and have been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[48]

7.1.1 Search strategy

A systematic literature search was conducted in 4 biomedical databases (PubMed, Embase, Cochrane Library, International Network of Agencies for Health Technology Assessment [INAHTA] HTA database) up to 29 March 2022. The search strategy included filters to exclude non-human studies; non-English, non-French, non-Italian or non-German language studies; and specific publication types outlined in ***Table 3*** (i.e. editorials, letters to the editor, news articles and conference abstracts). No other filters were used during the searches. Searches were also conducted in ClinicalTrials.gov and the EU Clinical Trials Register to identify unpublished and ongoing clinical trials related to the treatment of NVAF with DOACs. ***Table 59*** (***Appendix A***) outlines the full search strategy for each database.

7.1.2 Study selection

The literature search initially focused on retrieving existing systematic reviews with network meta-analyses (NMA) or meta-analyses that assessed the clinical efficacy, effectiveness and safety of DOACs compared to VKAs. Existing systematic reviews were considered up to date if any studies published after their search dates (as identified from the searches conducted for the present HTA) were unlikely to significantly change the magnitude or direction of the results. This was investigated by considering the sample size, reported treatment effect size and variance against the meta-analysis results of the existing reviews.

Where eligible systematic reviews were not available, primary studies meeting the PICO criteria were included. Additionally, the searches sought to identify relevant literature relating to ethical, social, organisational and legal issues, including systematic reviews, RCTs, NRSIs, ethnographic studies, phenomenological studies and narrative research articles.

Results from the literature searches were imported into Rayyan (Rayyan Systems Inc, United States).[49] Rayyan functions similarly to EndNote but allows for easy blinding of reviewers and management of study inclusion conflicts.[49] The search results were screened against the predetermined eligibility criteria

(***Table 3***) by 2 reviewers in multiple phases. To ensure that the inclusion criteria were interpreted consistently between reviewers, training samples of 250 citations were used to establish inter-rater reliability. Both reviewers selected studies independently in duplicate for each training sample, and selections were then compared between reviewers. The first sample was a training sample only, and the subsequent samples were used to calculate inter-rater reliability; a minimum Cohen's Kappa score of 0.7, representing substantial agreement between reviewers,[50] was required. In total, 6 training samples totalling 1,500 citations were needed to establish a Kappa score of 0.855, after which point screening of the remainder of articles by title and abstract was split between the reviewers. In cases where a reviewer was unsure about whether to include an article, the article was included for further review by full text. Following the title and abstract screen, all articles deemed potentially relevant were reviewed in full text by each reviewer independently, in duplicate. Conflicts between reviewers on study inclusion were settled via consensus. If consensus was not reached, a third reviewer decided whether to include or exclude the citation. Reference lists of included studies were searched (pearled) to identify additional relevant studies.

Table 3 Study selection criteria

	Inclusion criteria	Exclusion criteria
Population	Patients with NVAF (AF in the absence of moderate/severe mitral stenosis or a mechanical prosthetic heart valve) who are eligible for oral anticoagulation	
Intervention(s)	**DOAC** 1. Dabigatran (Pradaxa®) – 110–150 mg twice daily 2. Apixaban (Eliquis®) – 2.5–5 mg twice daily 3. Edoxaban (Lixiana®) – 30–60 mg once daily 4. Rivaroxaban (Xarelto®) – 15–20 mg once daily	Non-oral preparations; betrixaban
Comparator(s)	**VKA** 1. Acenocoumarol (Sintrom®) – 1–8 mg once daily 2. Phenprocoumon (Marcoumar®) – 1.5–4.5 mg once daily 3. Warfarin – 1.5–12 mg once daily [a]	Non-oral preparations; warfarin as a comparator in NRSI; suboptimal therapeutic VKA dosing (target INR <2 or >3)
Outcome(s)	**Clinical outcomes** 1. All-cause mortality 2. Cardiovascular-related mortality 3. Bleeding: a. Major/life-threatening bleeding b. Intracranial bleeding c. Gastrointestinal bleeding d. Clinically-relevant bleeding (i.e. requiring intervention) 4. Systemic embolic event 5. Stroke: a. Ischaemic stroke	Incomplete reporting (i.e. missing data that could not be imputed)

	Inclusion criteria	Exclusion criteria
	b. Haemorrhagic stroke 6. Cognitive functioning 7. Adherence: the extent to which the consumer conforms to the agreed behaviours, with respect to timing dosage and frequency of medication-taking[43] 8. Persistence: the duration of time from initiation to discontinuation of therapy[43] 9. Health-related quality of life 10. Treatment discontinuation due to adverse events **Health economic outcomes** 1. Direct medical technology costs of the technology and related events (resource use valuation) 2. Cost-effectiveness/cost-utility 3. Budget-impact	
Design/Publication type	**Clinical evidence** Systematic reviews with NMA or meta-analysis [b] of RCTs and NRSIs. Where suitable reviews are not available, RCTs and NRSIs were included. **Economic evidence** Cost-effectiveness/utility analyses, budget impact analysis, cost analysis **Social, legal, ethical and organisational evidence** Systematic reviews, RCTs, NRSI, ethnographic studies, phenomenological studies, and narrative research articles	Single-arm studies, case reports, conference abstracts, letters to the editor, expert opinions, editorials, narrative review articles
Language	English, French, Italian and German language studies[51]	
Country	WHO Mortality Stratum A [c]	
Year	All	

Abbreviations

AF: atrial fibrillation; **DOAC**: direct oral anticoagulant; **INR**: International normalised ratio; **NMA**: network meta-analysis; **NRSI**: non-randomised studies of interventions; **NVAF**: non-valvular atrial fibrillation; **RCT**: randomised controlled trial; **VKA**: vitamin K antagonist; **WHO**: World Health Organization.

Notes

[a] Studies on warfarin were considered for inclusion where there was no evidence for phenprocoumon or acenocoumarol.

[b] Up to date was defined as a systematic review that captured enough contemporary evidence such that any studies published after the search dates are unlikely to substantially change the magnitude or direction of the results of the review. Quality was evaluated against the AMSTAR-II appraisal criteria.[52] Articles with no critical insufficiencies (in relation to selection criteria, search strategy etc) were eligible for inclusion.

[c] WHO Stratum A countries include Andorra, Australia, Belgium, Brunei, Canada, Croatia, Cuba, Cyprus, Czech Republic [Czechia], Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, the Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom [UK], and United States of America [USA]. Only studies based in WHO-Mortality-Stratum A countries will be included. Studies based outside of WHO-Mortality-Stratum A countries were excluded during full-text screening because the cause of death and burden of disease in these countries are not comparable to those in Switzerland.[53] Multi-country studies that included studies outside WHO Stratum A were only included if at least 80% of the sample were from Stratum A countries.

7.1.3 Data extraction

One reviewer independently extracted data (on a study-arm level, where applicable) into a standardised template, which was checked against the original study record by a second reviewer. Disagreements were settled by discussion or utilisation of a third independent reviewer. Data of interest included:[46,54]

- Study information: study-arm, study identifier, location, date, number of institutions, setting (i.e. hospital, community care etc.), study design, length of follow-up, inclusion/exclusion criteria, study author.
- Demographic information: number of participants, age, sex, ethnicity, body mass index, comorbidities (e.g. hypertension, chronic heart failure, impaired renal function), $CHADS_2$ score, CHA_2DS_2-VASc score, HAS-BLED score, diagnosis (i.e. type of AF), prior myocardial infarction (MI), prior stroke or transient ischaemic attack (TIA).
- Intervention and comparator: drug name, dose, frequency of administration, concomitant and prior interventions, INR testing method (e.g. patient self-testing, provider), time in therapeutic range.
- Outcomes of interest: number of events, time-to-event data, and baseline, final or change from baseline scores with standard deviations in any of the aforementioned outcomes (***Table 2***).
- Any noteworthy features (e.g. effect modifiers), limitations or differences in the study.

For studies that reported outcomes graphically, *WebPlotDigitizer* was used to convert graph points into numerical values.[55]

7.1.4 Assessment of quality of evidence

The assessment of the quality of evidence was performed by 2 reviewers in duplicate. Differences were settled via consensus. The quality and risk of bias of included evidence was assessed using different tools depending on the research design. Systematic reviews were evaluated against the AMSTAR-II appraisal criteria,[52] RCTs were evaluated using Cochrane Risk of Bias 2.0 (RoB 2.0)[56] and NRSI were evaluated using the Cochrane Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) tool.[57] Quality assessments of primary studies conducted in included systematic reviews were not repeated unless they were conducted with a tool not listed above. As such, RoB 2.0 appraisals conducted by the National Institute for Health and Care Excellence (NICE) 2020 were adapted for the current HTA report.[58]

The overall certainty of the reported outcomes was appraised using the GRADE approach.[59] The certainty of evidence supporting an outcome, as scored according to the GRADE approach, is defined into the following categories:[60]

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty**: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- **Very low certainty**: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

A summary-of-findings table based on the available RCT evidence has been produced for the 7 key outcomes (following GRADE recommendations). The key outcomes are listed below:

1. All-cause mortality
2. Major/life-threatening bleeding
3. Stroke or systemic embolic event
4. Ischaemic stroke
5. Intracranial bleeding
6. Adherence to treatment plan
7. Discontinuation due to adverse events

7.1.5 Data analyses of efficacy, effectiveness and safety outcomes

7.1.5.1 Data synthesis

The planned method of data synthesis was dependent on whether relevant systematic reviews with NMAs or meta-analyses were available. *De novo* analysis was planned only if no existing systematic reviews met the inclusion criteria (***Table 3***). The results for the relevant outcomes reported by the included systematic review was adapted, meaning outcome data was extracted from the review and re-analysed according to the analysis methods described below in order to standardise the analytical approach for this report, and to present the analyses in combined forest plots per-outcome.

Where existing systematic review evidence could be adapted, or was not available, pairwise meta-analyses comparing individual DOACs to the VKA class of drugs were performed separately for RCT and NRSI studies. Meta-analysis was performed using Review Manager (version 5.4.1).[61] Random-effects models using the generic inverse variance method were used as the basis for the analysis. Meta-analysis was performed for outcomes reported by at least 2 studies, per DOAC versus VKA class comparison. The results for each individual DOAC versus VKA class comparison have been grouped in a single forest plot per outcome.

Except for health-related quality of life (HRQoL), all outcomes included in the review were dichotomous. Each dichotomous outcome has been reported as either a risk ratio (RR) or hazard ratio (HR) with 95% confidence intervals (95% CI). The choice of which outcome measure was used in each meta-analysis was directed by the availability of evidence (i.e. most RCTs reported relative events as RR; most NRSIs reported relative events as HR). HRQoL has been reported as mean difference between treatment arms with 95% CIs. All outcomes have been reported at longest follow-up.

7.1.5.2 Assessment of heterogeneity

Heterogeneity was assessed graphically through the presentation of forest plots, and statistically using the Chi^2 test ($p < 0.10$ representing significant heterogeneity) and the I^2 statistic for the meta-analysis of dichotomous outcomes, and Tau^2 and I^2 for continuous outcomes. The thresholds for low, moderate, substantial and considerable heterogeneity were adopted from the Cochrane handbook (i.e. I^2 = 0–40% might not be important; 30–60% moderate; 50–90% substantial; 75–100% considerable heterogeneity).[47] Where substantial heterogeneity was evident, the causes of this was explored through subgroup analysis, where possible, as described in ***Section 7.1.5.4***.

7.1.5.3 Publication bias

Publication bias was not assessed quantitatively because none of the analyses included at least 10 studies.[47]

7.1.5.4 Subgroup and sensitivity analysis

Subgroup analyses were planned to investigate potential causes of heterogeneity based on the following potential effect modifiers from meta-analyses of RCTs:

- age, per decade above 50[62]
- sex[62]
- body mass index[62]
- hypertension[62]
- previous stroke or transient ischaemic attack[62]
- previous myocardial infarction[62]
- chronic heart failure[62]
- impaired renal function[62]
- $CHADS_2$ score[62]
- CHA_2DS_2-VASc score[62]
- HAS-BLED score.[62]

Sensitivity analyses were planned to investigate the impact of methodological factors on the reported results of the clinical evidence evaluation of RCTs.[46] These included:

- risk of bias due to selection bias
- risk of bias due to information bias
- follow-up duration.

These subgroup and sensitivity analyses could not be conducted owing to the limited data identified in the review.

7.1.5.5 Imputation methods for dealing with missing values

Missing standard errors were obtained from available HRs and 95% CIs using formulae detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.1)* and calculated using the calculator function in Review Manager (version 5.4.1).[47,61]

7.1.5.6 Narrative synthesis

If fewer than 2 studies reported an outcome, meta-analysis was not possible. In such cases, the results were plotted in a forest plot and described narratively but no analysis was conducted. For continuous outcomes, the mean change from baseline or final follow-up score and standard deviation were reported for each study arm, as well as the mean difference and 95% CI comparing the mean effects between groups. For dichotomous outcomes, event rates for each trial arm were reported, along with RR and 95% CI comparing the event rates between groups. All extracted data used in the analyses are available in ***Appendix B***.

7.1.6 Deviations from the HTA protocol

There were several methodological changes made from the HTA protocol:

1. The outcome defined in the protocol as “systemic embolic events” was broadened to include “stroke or systemic embolic events” owing to the availability of data in the included studies.
2. The outcome defined in the protocol as “serious adverse events” was changed to “discontinuations due to adverse events”, owing to heterogeneity in how adverse events were classified by the included studies.
3. The protocol stated that dichotomous outcomes would be reported as RRs. In the HTA, outcomes were reported as either a RR or a HR, owing to the availability of data. In many cases, studies reported HR in the absence of event rates, and as such RRs could not be calculated.
4. The protocol stated that the analyses would be conducted in RStudio. The analyses in the HTA were conducted in Review Manager due to changes in the authorship team, which resulted in a change in the authors’ skills and experience in using RStudio.

5. The protocol stated that GRADE summary of findings tables would be reported for RCT and NRSI analyses. In the HTA, GRADE summary of findings tables have been reported for RCT analyses but not NRSI analyses. Justification for this decision is provided in ***Section 7.2.5***. All GRADE evidence profile tables, for both RCTs and NRSIs, are presented in ***Appendix C***.
6. The protocol stated that a GRADE summary of findings would be reported for cardiovascular-related mortality. In the HTA, a GRADE summary of findings table has been presented for all-cause mortality instead of cardiovascular-related mortality, as this provides a better representation of the overall benefits and/or risks associated with each medication.
7. The protocol stated that a GRADE summary of findings table would be presented for haemorrhagic stroke. In the HTA, a GRADE summary of findings table has been presented for intracranial bleeding instead of haemorrhagic stroke, owing to the limited reporting of haemorrhagic stroke in the included studies.

7.2 Results: effectiveness, efficacy and safety

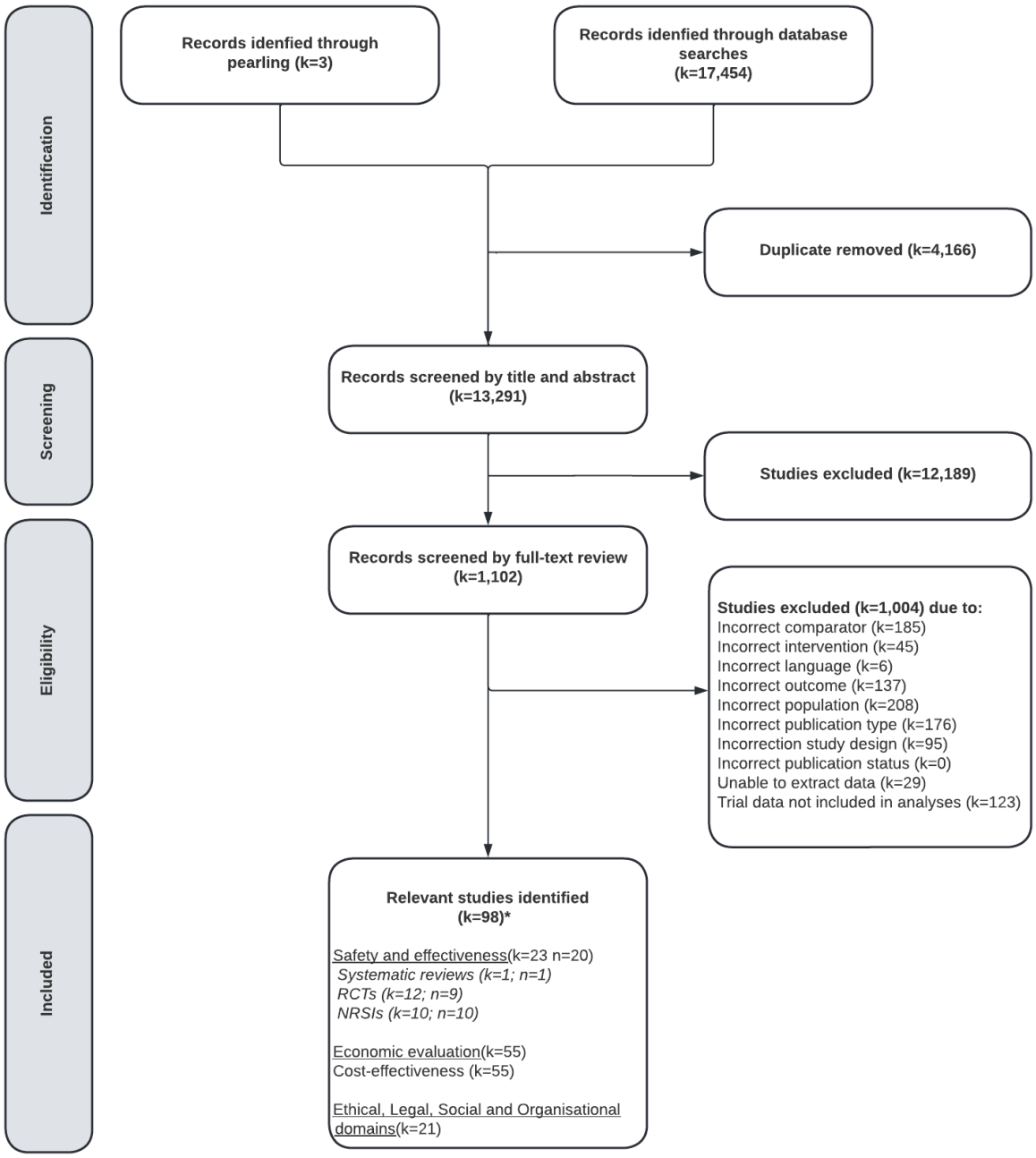
7.2.1 Search results

The systematic searches yielded 17,454 records plus 3 identified via pearling (***Section 7.1.2***). After duplicate removal, 13,291 articles were screened by title and abstract, 1,102 were screened by full text, and 98 met the inclusion criteria. The studies meeting the pre-determined inclusion criteria comprised 1 existing systematic review and/or meta-analysis, 12 RCT publications reporting on 9 unique RCTs, 10 NRSI publications reporting on 10 unique NRSIs, 55 cost-effectiveness studies and 21 studies relevant to the ethical, legal, social and organisational domains. It is important to note that although many RCT publications have been included per-trial because they meet the inclusion criteria, the primary study publication was used as the basis for the evaluation in most cases. A list of all articles excluded after full-text review is available from the authors upon request.

7.2.2 PRISMA flow diagram

The results of the systematic literature searches are summarised in ***Figure 1.***

Figure 1 PRISMA flow diagram



Abbreviations:

k: number of publications; **n**: number of trials; **NRSI:** non-randomised studies of interventions; **RCT:** randomised control trial.

Notes

* A single publication could be deemed relevant to multiple domains.

7.2.3 Study characteristics and risk of bias

7.2.3.1 Systematic review evidence

Of the existing systematic reviews with meta-analyses that were identified as meeting the inclusion criteria, the most up-to-date, comprehensive review was conducted by NICE, all other identified reviews were excluded.[58] The review appraised using the AMSTAR 2 checklist, and consistently scored positively against the relevant appraisal domains (***Table 4***).

All of the RCTs identified in the literature search were also included in the recent NICE evidence review (published in April 2021),[58] suggesting that no new evidence has been published. Due to this, the NICE evidence review was used as the basis for clinical evidence evaluation where possible, noting that the NICE review included a broader list of included studies, as it was not restricted to WHO Mortality Stratum A countries.

The results of the NICE review have been adapted to the current evaluation in 2 main ways. First, the quality appraisal of the RCTs included in both the present HTA and the NICE report were adapted from the NICE review (i.e. RoB 2.0 scores were adapted, GRADE scores were not). Second, analyses from the NICE review that included the same eligible studies as the current HTA were adapted by extracting the relevant outcome data for the individual DOAC versus VKA class comparisons, and re-analysing them in a single forest plot per outcome using the method described in Section ***7.1.5.1***; all of the analyses that used data from the NICE report have been re-analysed to account for the differences in interventions and analytical methods between the NICE review and the present HTA.

Table 4 AMSTAR 2 appraisal of NICE evidence review

AMSTAR 2 domain	NICE review
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Y
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Y
4. Did the review authors use a comprehensive literature search strategy?	PY
5. Did the review authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	Y
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Y
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y
10. Did the review authors report on the sources of funding for the studies included in the review?	Y
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Y
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y

AMSTAR 2 domain	NICE review
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Y
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Y

Abbreviations

N: no; **NA**: not applicable; **P**: partial; **PICO**: population, intervention, comparator, outcomes; **RoB**: risk of bias; **Y**: yes.

7.2.3.2 RCT: Study characteristics

Of the 26 trials included in the NICE evidence review, 13 were used in the pairwise analysis of direct evidence that compared DOAC with warfarin dosed to achieve a target INR of 2.0–3.0. The aim of all studies was to assess the relative efficacy of different anticoagulants for people with NVAF. ***Table 5*** summarises the evidence base identified in the NICE evidence review and in the independent searches undertaken for the current assessment. For the comparison of DOAC with warfarin, a total of 3 additional studies were identified by the NICE evidence review.[63-65]

In the systematic literature search undertaken for the current assessment, all published trials as included in the NICE evidence review were identified, with no additional trials uncovered. A small number of additional publications from ongoing trials were identified for ARISTOTLE,[66] ENGAGE-AF,[67-71] RE-LY[72] and ROCKET AF.[73] A published protocol for a new RCT comparing apixaban to phenprocoumon in patients with AF on chronic haemodialysis was identified, although no published data from this trial is available to date.[74] Data from Yamaguchi et al 2010, identified in the searches for clinical trials, remain unpublished. Therefore, the evidence-base is unchanged since publication of the NICE evidence review.

Table 5 List of included RCTs

Trial ID	Interventions	Inclusion in NICE pairwise evaluation	Inclusion in current HTA
ARISTOTLE 2011[75]	Apixaban 5 mg twice daily [a] Warfarin INR 2-3	Yes	Yes
ARISTOTLE-J 2011[76]	Apixaban 2.5 mg twice daily Apixaban 5 mg twice daily Warfarin INR 2-3	Yes	Yes
Chung et al 2011[77]	Edoxaban 30 mg once daily Edoxaban 60 mg once daily Warfarin INR 2-3	Yes	No [b]
ENGAGE AF 2013[78]	Edoxaban 30 mg once daily Edoxaban 60 mg once daily Warfarin INR 2-3	Yes	Yes
J-ROCKET AF 2012[79]	Rivaroxaban 15 mg once daily [c] Warfarin INR 2-3	Yes	Yes

Trial ID	Interventions	Inclusion in NICE pairwise evaluation	Inclusion in current HTA
Ke et al 2019[63]	Rivaroxaban 20 mg once daily Warfarin INR 2-3	Yes	No [d]
Mao et al 2014[64]	Rivaroxaban 20 mg once daily Warfarin INR 2-3	Yes	No [e]
PETRO 2007[80]	Dabigatran 150 mg twice daily [f] Warfarin INR 2-3	Yes	Yes
RE-LY 2009[81,82]	Dabigatran 110 mg twice daily Dabigatran 150 mg twice daily Warfarin INR 2-3	Yes	Yes
ROCKET AF 2011[83]	Rivaroxaban 20 mg once daily [g] Warfarin INR 2-3	Yes	Yes
Shosha et al 2017[65]	Rivaroxaban 20 mg once daily Warfarin INR 2-3	Yes	No [h]
Weitz et al 2010[84]	Edoxaban 30 mg once daily Edoxaban 60 mg once daily [i] Warfarin INR 2-3	Yes	Yes
Yamashita et al 2012[85]	Edoxaban 30 mg once daily Edoxaban 60 mg once daily [j] Warfarin INR 2-3	Yes	Yes

Abbreviations:

INR: international normalised ratio; **VKA:** vitamin K antagonist

Notes:

[a] <5% patients, who had additional risk factors, were given 2.5 mg twice daily

[b] Excluded as the population was from China, Republic of Korea, Singapore, Taiwan non-Stratum A country

[c] 22.1% patients, who had creatinine clearance 30–49ml/min, were given 10mg once daily

[d] Excluded as the population was from China, a non-Stratum A country

[e] Excluded as the population was from China, a non-Stratum A country

[f] Trial also included additional interventions of 150 mg twice daily with 81 or 325 mg aspirin, and 50 or 300mg twice daily dabigatran with and without aspirin

[g] 21.1% patients, who had creatinine clearance <50ml/min, were given 15 mg once daily

[h] Excluded as the population was from Egypt, a non-Stratum A country

[i] Trial also included additional interventions of edoxaban 30 mg twice daily and edoxaban 60 mg twice daily

[j] Trial also included the additional intervention of edoxaban 45 mg

A summary of included RCTs[75,76,78-85] is shown in ***Table 6***. Non-standard doses of DOACs, and co-interventions with aspirin, are not reported.

The majority of trials were conducted across multiple sites: 4 trials were conducted in multiple countries including sites in Switzerland (ARISTOTLE, ENGAGE-AF, ROCKET AF, RE-LY);[75,78,81-83] 2 trials were from Asian countries (ARISTOTLE-J, J-ROCKET AF),[76,79] and 2 had international sites including European countries but not Switzerland (Weitz et al 2010, PETRO 2007).[80,84]

Across the populations of interest, the total number of participants across all trials included in the analysis was 74,472 (warfarin versus apixaban: n=18,423; warfarin versus edoxaban: n=22,224; warfarin versus rivaroxaban: n=15,542; warfarin versus dabigatran: n=18,283).

Follow-up duration was reported at 3 months by 4 trials; other trials reported a follow-up of 19.4 to 30 months (ARISTOTLE, ENGAGE-AF, J-ROCKET AF, ROCKET AF, RE-LY).[75,78,79,81-83]

The mean time in therapeutic range (TTR) in the included RCTs ranged between 57.2% and 83.0% (median 62.2%); notably, all but one included trial reported a TTR below the recommended range of 70%.[86]

Table 6 Characteristics of included RCTs assessing clinical effectiveness and safety of oral anticoagulants

Study Trial Country	Study design Treatment duration	Population	Intervention(s) Sample size	Mean age (years)	Outcome(s)	Funding
ARISTOTLE 2011[75] NCT00412984 42 countries North and South America, Europe (including Switzerland), Russia, Israel, Australia, Asia and South Africa	RCT, double-blind Multicentre (1,113 sites) 21.6 months (median)	NVAF or flutter ECG diagnosed Warfarin INR 2–3 Mean TTR 62.2%	Total n = 18,201 Apixaban 5 mg twice daily n = 9,120 Warfarin n = 9,081	Total population, median 70 (IQR 63-76)	• Stroke or SE • All-cause mortality • Major/life-threatening bleeding • ICH • GI bleeding • Adherence • CV-related mortality • Haemorrhagic stroke • Ischaemic stroke • Persistence • Discontinuation due to AEs	Bristol-Myers Squibb and Pfizer
ARISTOTLE-J 2011[76] NCT00787150 1 country Japan	RCT, double-blind for dose, open-label for warfarin Multicentre (18 sites) 3 months	NVAF Diagnosis based on ECG, Holter recording or intracardiac electrogram Warfarin INR 2–3 (2–2.6 in ≥ 70 years) Mean TTR 60%	Total n = 222 Apixaban 2.5 mg twice daily n = 74 Apixaban 5 mg twice daily n = 74 Warfarin n = 74	Total population, mean 70.3 (SD NR) Apixaban 2.5 mg mean 69.3 Apixaban 5 mg mean 70 Warfarin mean 71.7	• Stroke or SE • All-cause mortality • Clinically-relevant bleeding • Major/life-threatening bleeding • Persistence • Discontinuation due to AEs	Bristol-Myers Squibb and Pfizer

Study Trial Country	Study design Treatment duration	Population	Intervention(s) Sample size	Mean age (years)	Outcome(s)	Funding
ENGAGE AF 2013[78] NCT00781391 46 countries North and South America, Europe (including Switzerland), Russia, Israel, Australia, Asia, South Africa	RCT, double-blind Multicentre (1,016 sites) 29.8 months (median)	NVAF ECG diagnosed $CHADS_2 \geq 2$ Warfarin INR 2–3 Mean TTR 64.9%	Total n = 21,105 Edoxaban 30 mg once daily n =7,034 Edoxaban 60 mg once daily n = 7,034 Warfarin n = 7,036	NR Inclusion age ≥ 21	• Stroke or SE • All-cause mortality • Clinically-relevant bleeding • Major/life-threatening bleeding • ICH • GI bleeding • Adherence • CV-related mortality • Haemorrhagic stroke • Ischaemic stroke • Persistence • Discontinuation due to AEs	Daiichi Sankyo Pharma Development
Weitz et al 2010[84] NCT00504556 12 countries North and South America, Europe (not Switzerland) & Russia	RCT, double-blind Multicentre (91 sites) 3 months	Persistent NVAF ECG diagnosed $CHADS_2 \geq 2$ Warfarin INR 2–3 Mean TTR 49.7%	Total n = 719 after exclusion of 427 patients on 30 mg and 60 mg edoxaban twice daily Edoxaban 30 mg once daily n = 235 Edoxaban 60 mg once daily n = 234 [b] Warfarin n = 250	Total population 65.1 (SD NR) Edoxaban 30 mg 65.2 Edoxaban 60 mg 64.9 Warfarin 66.0	• Stroke or SE • All-cause mortality • Clinically-relevant bleeding • Major/life-threatening bleeding • CV-related mortality • Persistence	Daiichi Sankyo Co., Ltd., Tokyo, Japan

Study Trial Country	Study design Treatment duration	Population	Intervention(s) Sample size	Mean age (years)	Outcome(s)	Funding
Yamashita et al 2012[85] Trial ID not disclosed 1 country Japan	RCT, double-blind for dose, open-label for warfarin Multicentre (61 sites) 3 months	NVAF ECG diagnosed $CHADS_2 \geq 1$ Warfarin INR 2–3 (1.6–2.6 in ≥70 years) Mean TTR 83% (≥70 years), 73% (<70 years)	Total n = 536,401 after exclusion of edoxaban 45 mg Edoxaban 30 mg once daily n = 135 Edoxaban 60 mg once daily n = 132 [c] Warfarin n = 134	Total population NR Inclusion age ≥ 20 Edoxaban 30 mg 69.4 Edoxaban 60 mg 68.4 VKA 68.8	• Stroke or SE • All-cause mortality • Major/life-threatening bleeding • Persistence	Daiichi Sankyo Co., Ltd., Tokyo, Japan
J-ROCKET AF 2012[79] NCT00494871 1 country Japan	RCT, double-blind Multicentre (165 sites) 30 months	NVAF ECG diagnosed Warfarin INR 2–3 (INR 1.6–2.6 in ≥70 years) Mean TTR 65%	Total n = 1,280 Rivaroxaban 15 mg once daily [d] n = 639 Warfarin n = 639	Total population 71.1 (range 34–90)	• Stroke or SE • All-cause mortality • ICH • GI bleeding • Adherence • Haemorrhagic stroke • Ischaemic stroke • Persistence	Bayer Yakuhin Ltd

Study Trial Country	Study design Treatment duration	Population	Intervention(s) Sample size	Mean age (years)	Outcome(s)	Funding
ROCKET AF 2011[83] NCT00403767 44 countries North and South America, Europe (including Switzerland), Russia, Israel, Australia, New Zealand, Asia, South Africa	RCT, double-blind Multicentre (959 sites) Median 19.4 months	NVAF ECG diagnosed $CHADS_2 \geq 2$ Warfarin INR 2–3 Mean TTR 55%	Total n = 14,264 Rivaroxaban 20 mg once daily [e] n = 7,131 Warfarin n = 7,133	Total population, median 73 (IQR 6–78)	• Stroke or SE • All-cause mortality • Clinically-relevant bleeding • Major/life-threatening bleeding • ICH • GI bleeding • Adherence • CV-related mortality • Haemorrhagic stroke • Ischaemic stroke • Persistence • Discontinuation due to AEs	Johnson & Johnson and Bayer
PETRO 2007[80] NCT01227629 4 countries USA, Denmark, the Netherlands and Sweden	RCT, double-blind for dabigatran dose but open-label for concomitant aspirin and warfarin Multicentre (38 locations) 3 months	Permanent, persistent, and paroxysmal NVAF with coronary artery disease Diagnosis not explained Warfarin INR 2–3 Mean TTR 57.2%	Total n = 502 (515 patients reported) Dabigatran 150 mg twice daily n = 100 [f] Warfarin n = 70	Total population 69.5	• Stroke or SE • Clinically-relevant bleeding • Major/life-threatening bleeding • Discontinuation due to AEs	Boehringer Ingelheim Pharmaceuticals

Study Trial Country	Study design Treatment duration	Population	Intervention(s) Sample size	Mean age (years)	Outcome(s)	Funding
RE-LY 2009[81,82] NCT00262600 44 countries North and South America, Europe (including Switzerland), Russia, Israel, Australia, Asia, South Africa	RCT, open-label (blinded for DOAC, open for warfarin) Multicentre (984 sites) Mean 24 months	NVAF ECG diagnosed Mean CHADS2 = 2.1 Warfarin INR 2–3 Mean TTR 64%	Total n = 18,113 Dabigatran 110 mg twice daily n = 6,015 Dabigatran 150 mg twice daily n = 6,076 Warfarin n = 6,022	Total population mean 71.5 (SD 8.7)	• Stroke or SE • All-cause mortality • Major/life-threatening bleeding • ICH • GI bleeding • Adherence • CV-related mortality • Haemorrhagic stroke • HRQoL • Ischaemic stroke • Persistence • Discontinuation due to AEs	Boehringer Ingelheim

Abbreviations:

AF: atrial fibrillation; **CV:** cardiovascular; **ECG:** electrocardiogram; **GI:** gastrointestinal; **HRQoL:** health-related quality of life; **INR:** international normalised ratio; **ICH:** intracranial haemorrhage; **IQR:** interquartile range; **NR:** not reported; **NVAF:** non-valvular atrial fibrillation; **TTR:** time in therapeutic range; **RCT:** randomised controlled trial; **SD:** standard deviation; **SE**: systemic embolism; **VKA:** vitamin K antagonist

Notes:

The study characteristics were extracted from the NICE evidence review and Lopez-Lopez et al 2017[44,58]

[a] <5% patients, who had additional risk factors, were given 2.5 mg twice daily

[b] Trial also included additional interventions of edoxaban 30 mg twice daily and edoxaban 60 mg twice daily

[c] Trial also included the additional intervention of edoxaban 45 mg

[d] 22.1% patients, who had CrCl 30-49ml/min, were given 10mg once daily

[e] 21.1% patients, who had CrCl <50ml/min, were given 15 mg once daily

[f] Trial also included additional interventions of 150 mg twice daily with 81 or 325 mg aspirin; and 50 or 300mg twice daily dabigatran with and without aspirin

7.2.3.3 RCT: Risk of bias

As assessed using the Cochrane RoB 2.0 tool, a summary of the risk of bias for all included trials as adapted from the NICE evidence review is shown in ***Table 7***.[58] When adapting NICE's risk of bias scores, the overall risk of bias for studies that NICE reported as "very high" was downgraded to "high", because a "very high" rating does not align with the RoB 2.0 tool.

Across all trials, risk of bias was low for outcome reporting and outcome measurements. ENGAGE AF and ROCKET AF were deemed to be overall at a low risk of bias. Weitz et al 2010 was at an overall low risk of bias for the outcomes of clinically-relevant bleeding and major/life-threatening bleeding.

The ARISTOTLE-J and PETRO studies and Yamashita et al 2012 were all at very high risk of bias overall due to a high risk of bias across multiple domains. A high risk of bias for selection was related to a lack of clarity or not enough information regarding the randomisation process or allocation concealment. For blinding, the risk of bias was high due to studies being open-label for the comparison of DOAC versus warfarin. Where reported, all studies were blinded for the dose of DOAC.

Table 7 Risk of bias in the included RCTs

Trial ID	Overall risk of bias	RoB arising from the randomisation process	RoB due to deviations from the intended interventions	Missing outcome data	RoB in measurement of the outcome reporting	RoB in selection of the reported result
ARISTOTLE, 2011 [75]	x	x	+	+	+	+
ARISTOTLE-J, 2011 [76]	x	x	x	x	+	+
ENGAGE AF, 2013 [d78]	+	+	+	+	+	+
J-ROCKET AF, 2012 [79]	x	x	+	+	+	+
PETRO, 2007 [80]	x	x	x	x	+	+
RE-LY, 2009 [81]	x	+	x	+	+	+
ROCKET AF, 2011 [83]	+	+	+	+	+	+
Weitz, 2010 [84]	x	+	+	x	+	+
Yamashita, 2012 [85]	x	x	x	x	+	NR

Notes

+ = low risk; **x** = high risk; **–** = some concerns; **?** = no information.

Source

Adapted from NICE (2021)[58] The 'very high' overall RoB assigned to the ARISTOTLE-J 2011, PETRO 2007 and Yamashita 2012 trials has been downgraded to 'high' to map against the Cochrane RoB 2.0 tool.

7.2.3.4 NRSI: Study characteristics

In total, 10 unique NRSI publications were included, of which there were single-country studies from the Netherlands (k=2), Germany (k=4), Spain (k=2), and 2 multi-country studies; the first included centres from Canada, Denmark, Germany, Spain, United Kingdom; the other included centres from Austria, Bulgaria, Czech Republic, Estonia, Hungary, Israel, Latvia, Poland, Romania, Russian Federation, Serbia, and Slovenia.

The included NRSIs were all retrospective cohort studies, in which data were collected as part of a registry or clinical database/case-note review. All studies except for 2[87,88] reported a propensity score matched analysis, to adjust for possible confounding.

All the included studies included patients treated for AF or NVAF (n=1,772,002). Across the NRSIs, 8 evaluated apixaban (n=183,780), 9 evaluated dabigatran (n=144,742), 2 evaluated edoxaban (n=16,531) and 7 evaluated rivaroxaban (n=417,689). It is important to note that majority of the NRSIs did not report outcomes based on dosage, making naïve comparisons with the RCT data challenging.

The VKAs included in the NRSIs were predominantly phenprocoumon or acenocoumarol, noting that Paschke et al 2020.[89] included a small percentage of VKA patients treated with warfarin (0.5%), and van den Ham et al 2021.[87] included a small percentage of patients treated with fluindione (0.9%) and warfarin (14%).

The average length of follow-up in the NRSIs varied across studies, and across treatment groups within each study. As such, providing an accurate estimate of the average treatment duration is challenging. Specific treatment durations reported for each drug within each study are outlined in ***Table 8***.

Of note, the study by Mueller et al 2018 mentioned in ***Section 1*** was not included because it grouped DOACs as a class; it was not possible to separate out the individual DOACs.[3]

Table 8 Characteristics of included NRSI assessing clinical effectiveness and safety of oral anticoagulants

Study Trial Country	Study design Treatment duration	Population	Intervention(s) Sample size	Mean age (years) (SD)	Outcome(s)	Funding
Korenstra et al 2016[90] The Netherlands	Retrospective cohort 21.3 mo (median)	NVAF with stroke risk (CHADS2 VAS2 score ≥1 point) Mean TTR 78%	Total n=766 Dabigatran 110 mg twice daily: n=152 Dabigatran 150 mg twice daily: n=231 Acenocoumarol (INR:2.0-3.5): n=383	Dabigatran: 70.6 (8.9) Acenocoumarol: 72.3 (9.3)	• All-cause mortality • Cardiovascular-related mortality • Major/life threating bleeding • Intracranial bleeding • GI bleeding • Stroke and/or SE • Ischaemic stroke	Boehringer Ingelheim International
Paschke et al 2020[89] [a] Germany	Retrospective cohort DOAC: 20 mo (median) VKA: 15 mo quarters (median)	AF with no previous OAC use Mean TTR NR	Total: n= 837,430 Apixaban 2.5/5 mg (dose/day NR): n=131,748 Dabigatran 75-150 mg (dose/day NR): n=53,057 Edoxaban 15-60 mg (dose/day NR): n=14,276 Rivaroxaban 2.5–20 mg (dose/day NR): n=228,600 Phenprocoumon (INR: 1.5-3): n=345,156 Warfarin (INR: 1.5-3): n=2,083	DOAC: 75.7 (9.9) VKA: 75.8 (8.8)	• Clinically-relevant bleeding • Stroke and/or SE • Ischaemic stroke	NA

Study Trial Country	Study design Treatment duration	Population	Intervention(s) Sample size	Mean age (years) (SD)	Outcome(s)	Funding
Rodriguez-Bernal et al 2021[91] Spain	Retrospective cohort Apixaban: 10 mo (median) Dabigatran: 25 mo (median) Rivaroxaban: 18 mo (median) Acenocoumarol: 22 mo (median)	AF or atrial flutter Mean TTR NR	Total: n=41,560 Apixaban (dose NR): n=2,259 Dabigatran (dose NR): n=3,380 Rivaroxaban (dose NR): n=3,445 Acenocoumarol (target INR NR): n=32,476	Dabigatran: 72.3 (11.3) Rivaroxaban: 74.7 (10.6) Apixaban: 75.0 (10.7) Acenocoumarol: 74.8 (9.6)	• All-cause mortality • Major/life threating bleeding • Intracranial bleeding • GI bleeding • Ischaemic stroke	Instituto de Salud Carlos III Spanish Ministry of Health European Regional Development Fund
Ujeyl et al 2018[92] Germany	Retrospective cohort Dabigatran: 8 mo (mean) Rivaroxaban: 9 mo (mean) Apixaban: 8 mo (mean) Phenprocoumon: 10.0 mo (median)	NVAF Mean TTR NR	Total: n=215,068 Apixaban 2.5/5 mg twice daily: n=4,894 Dabigatran 110/150 mg twice daily: n=23,654 Rivaroxaban 15/20 mg once daily: n=59,449 Phenprocoumon (target INR NR): n=87,997	DOAC: 75.4 (9.6) Phenprocoumon: 75.4 (9.6)	• All-cause mortality • Major/life threating bleeding • Intracranial bleeding • GI bleeding • Ischaemic stroke • Treatment discontinuation due to adverse events • Cardiovascular-related mortality	AOK Bundesverband

Study Trial Country	Study design Treatment duration	Population	Intervention(s) Sample size	Mean age (years) (SD)	Outcome(s)	Funding
van den Ham et al 2021[87] Canada, Denmark, Germany, Spain, UK	Retrospective cohort Canada • DOAC:22 mo • VKA: 28 mo Denmark • DOAC: 11mo • VKA: 12 mo German • NR Spain • DOAC: 18 mo • VKA: 31 mo UK • DOAC: 10 mo • VKA: 32 mo	NVAF Mean TTR NR	Total: n= 476,973 Apixaban 10 mg: n=7,727 Dabigatran 150 mg: n=24,765 Rivaroxaban 20 mg: n=63,327 VKA (target INR NR): n=381,154 • Acenocoumarol: n=87,798 • Phenprocoumon: n=199,780 • Warfarin: n=93,576 • Fluindione: n= 2,762	Canada • DOAC: 77.1(8.9) • VKA: 76.1 (10.6) Denmark • DOAC: 73.4 (11.2) • VKA: 71.6 (11.2) Germany • DOAC: 74.8 (11.4) • VKA: 73.9 (9.6) Spain • DOAC: 75.6 (10.0) • VKA: 75.4 (10.8) UK • DOAC: 74.8 (11.0) • VKA: 73.8 (10.4)	• Intracranial bleeding • GI bleeding • Ischaemic stroke • Major/ life-threatening bleeding	Canadian Institutes of Health Research European Medicines Agency

Study Trial Country	Study design Treatment duration	Population	Intervention(s) Sample size	Mean age (years) (SD)	Outcome(s)	Funding
RE-SONANCE, 2020[88] Austria, Bulgaria, Czech Republic, Estonia, Hungary, Israel, Latvia, Poland, Romania, Russian Federation, Serbia, Slovenia	Prospective cohort 12 mo (median)	NVAF (no use of OAC within 1y prior) Mean TTR NR	Total n=5,365 Dabigatran 110/150 mg twice daily: n=3,179 VKA: n=2,186 • Acenocoumarol (target INR NR) • Warfarin (target INR NR)	Dabigatran: 68.6 (10.1) VKA: 68.5 (9.5)	• Major/life threating bleeding • Treatment discontinuation due to adverse events	Boehringer Ingelheim International
Warkentin et al 2022[93] Germany	Retrospective cohort 12 mo (mean)	AF (no prescription of OAC within 1y prior) Mean TTR NR	Total: n=41,903 Apixaban 5 mg twice daily: n=10,977 Dabigatran 150 mg twice daily: n=1,914 Edoxaban 60 mg once daily: n=2,255 Rivaroxaban 20 mg once daily: n=6,558 Phenprocoumon (target INR NR): n=20,179	DOAC: 77.5 (10.1) Phenprocoumon: 77.0 (8.9)	• All-cause mortality • Clinically-relevant bleeding • Stroke and/or SE	NA

Study Trial Country	Study design Treatment duration	Population	Intervention(s) Sample size	Mean age (years) (SD)	Outcome(s)	Funding
Zielinski et al 2020[94] The Netherlands	Retrospective cohort 48 months (median)	AF Mean TTR NR	Total n=87,412 Apixaban 2.5/5 mg twice daily: n=13,878 Dabigatran ≤150 mg twice daily: n=29,288 Rivaroxaban 15/20 mg once daily: n=34,167 VKA [b]: n=10,079	DOAC: 70 (11.0) VKA: 73 (11.0)	• Persistence	NA
Ramagopalan et al 2019[95] Spain	Retrospective cohort 12 mo (median)	NVAF Mean TTR NR	Total n=4,320 Apixaban 5 mg once daily: n=486 Apixaban 10 mg once daily: n=1,674 Acenocoumarol (target INR NR): n=2,160	Apixaban: 71.2 (12.8) Acenocoumarol: 71.6 (10.1)	• Major/life threating bleeding • Intracranial bleeding • GI bleeding • Stroke and/or SE • Ischaemic stroke • Persistence	Bristol-Myers Squibb Pfizer

Study Trial Country	Study design Treatment duration	Population	Intervention(s) Sample size	Mean age (years) (SD)	Outcome(s)	Funding
Hohnloser et al 2018[96] Germany	Retrospective cohort Phenprocoumon: 362 ± 275 days (mean) Apixaban: 306 ± 239 days (mean) Dabigatran: 339 ± 317 days (mean) Rivaroxaban: 340 ± 284 days (mean)	AF Mean TTR NR	Total n=61,205 Apixaban 2.5 mg: n=3,741 Apixaban 5 mg: n=6,376 Dabigatran 110 mg: n=2,596 Dabigatran 150 mg: n=2,526 Rivaroxaban 15 mg: n=6,220 Rivaroxaban 20 mg: n=15,923 Phenprocoumon (target INR NR): n=23,823	Apixaban 2.5 mg: 81.6 (8.2) Apixaban 5 mg: 70.4 (10.9) Dabigatran 110 mg: 77.3 (9.5) Dabigatran 150 mg: 66.0 (10.7) Rivaroxaban 15 mg: 79.1 (9.0) Rivaroxaban 20 mg: 69.3 (11.6) Phenprocoumon: 75.2 (9.5)	• Stroke and/or SE • Stroke and ischaemic stroke and haemorrhagic stroke • All-cause mortality • Major/ life-threatening bleeding • Intracranial bleeding • GI bleeding • Clinically-relevant bleeding	Bristol-Myers Squibb Pfizer

Abbreviations:

AF: atrial fibrillation, **DOAC:** direct oral anticoagulant; **GI:** gastrointestinal; **INR:** international normalization ratio; **mg:** milligrams; **mo:** months; **NA:** not applicable; **NR:** not reported; **NVAF:** non-valvular atrial fibrillation; **SD:** standard deviation; **SE**: systemic embolism; **TTR**: time in therapeutic range; **VKA:** vitamin K antagonist; **y**: years.

Notes:

All included trials only reported combined results for each drug dose and did not report the outcomes per dose (e.g. Apixaban 5.0 mg).

[a] This trial includes "non approved" doses of DOACs that are outside the scope of this HTA report. However, the sensitivity analysis in the trial found statistically significant difference when the doses that limited to "approved" doses.

[b] Specific VKA not reported; however, the study was conducted in the Netherlands so it is assumed that the VKA used was Acenocoumarol (most prevalent VKA).

7.2.3.5 NRSI: Risk of bias

As assessed with the ROBINS-I tool,[57] all included NRSIs were at either serious (k=8)[87,90-97] or critical (k=2)[88,89] risk of bias (***Table 9***). The biggest contributing factors to these rankings were unmeasured confounding and deviations from intended interventions.

Most studies took appropriate steps to adjust for possible confounding, either through propensity score matching, inverse probability weighting or regression; however, all studies had unmeasured confounding variables listed *a priori* in the HTA protocol and were thus rated as having a serious risk of bias. In particular, Vinereanu et al 2020[88] was at critical risk of bias due to confounding because the primary analysis was not appropriately adjusted for potential confounding.

Half of the included NRSIs reported significant deviations from the intended interventions and/or unbalanced deviations between groups, in the form of discontinuations from the assigned treatments. Most notably, Paschke et al 2020[89] reported discontinuation in 64.8% of VKA users and 21.5% of DOAC users; Ujeyl et al 2018[92] reported discontinuation in 20% of VKA users and 30–36% of DOAC users; and Ramogapalan et al 2019[95] reported discontinuation in 28.9% of apixaban users and 39.4% of acenocoumarol users.

Studies were generally appraised as having a low risk of bias for the remaining domains, with one notable exception. Vinereanu et al 2020[88] was rated as having a serious risk of bias regarding measurement of outcomes, specifically in relation to the patient-reported Perception on Anticoagulant Treatment Questionnaire, because it was not reported if the measurement of this outcome was blinded, though it could reasonably be assumed that it was not. For other outcomes, the study was at a low risk of bias for this domain.

Table 9 Risk of bias in the included NRSIs

Trial ID	Overall risk of bias	Confounding	Selection of participants	Classification of intervention	Deviations from interventions	Missing data	Measurement of outcomes	Selective reporting
Warkentin et al 2022[93]	✗	✗	?	+	+	+	+	+
Rodriguez-Bernal et al 2021[91]	✗	✗	+	+	?	+	+	+
van den Ham et al 2021[87]	✗	✗	+	+	+	+	+	+
Zielinksi et al 2020[94]	✗	✗	-	+	-	+	+	+
RE-SONANCE 2020[88]	✗ ✗	✗ ✗	+	+	+	+	✗ A +	+

Trial ID	Overall risk of bias	Confounding	Selection of participants	Classification of intervention	Deviations from interventions	Missing data	Measurement of outcomes	Selective reporting
Paschke et al 2020[89]	XX	X	+	+	X	?	+	+
Ramogapalan et al 2019[95]	X	X	-	+	X	+	+	+
Ujeyl et al 2018[92]	X	X	+	+	X	+	+	+
Korenstra et al 2016[90]	X	X	+	+	?	+	+	+
Hohnloser et al 2018[96]	X	X	+	+	+	+	+	+

Notes

+ = low risk; **–** = moderate risk; **x** = serious risk; **xx** = critical risk; **?** = no information.

Vinereanu et al 2020 was appraised as having a serious risk of bias due to measurement of outcomes for the patient-reported Perception on Anticoagulant Treatment Questionnaire because it was not reported if the measurement of this outcome was blinded; for other outcomes, the study was at a low risk of bias for this domain.

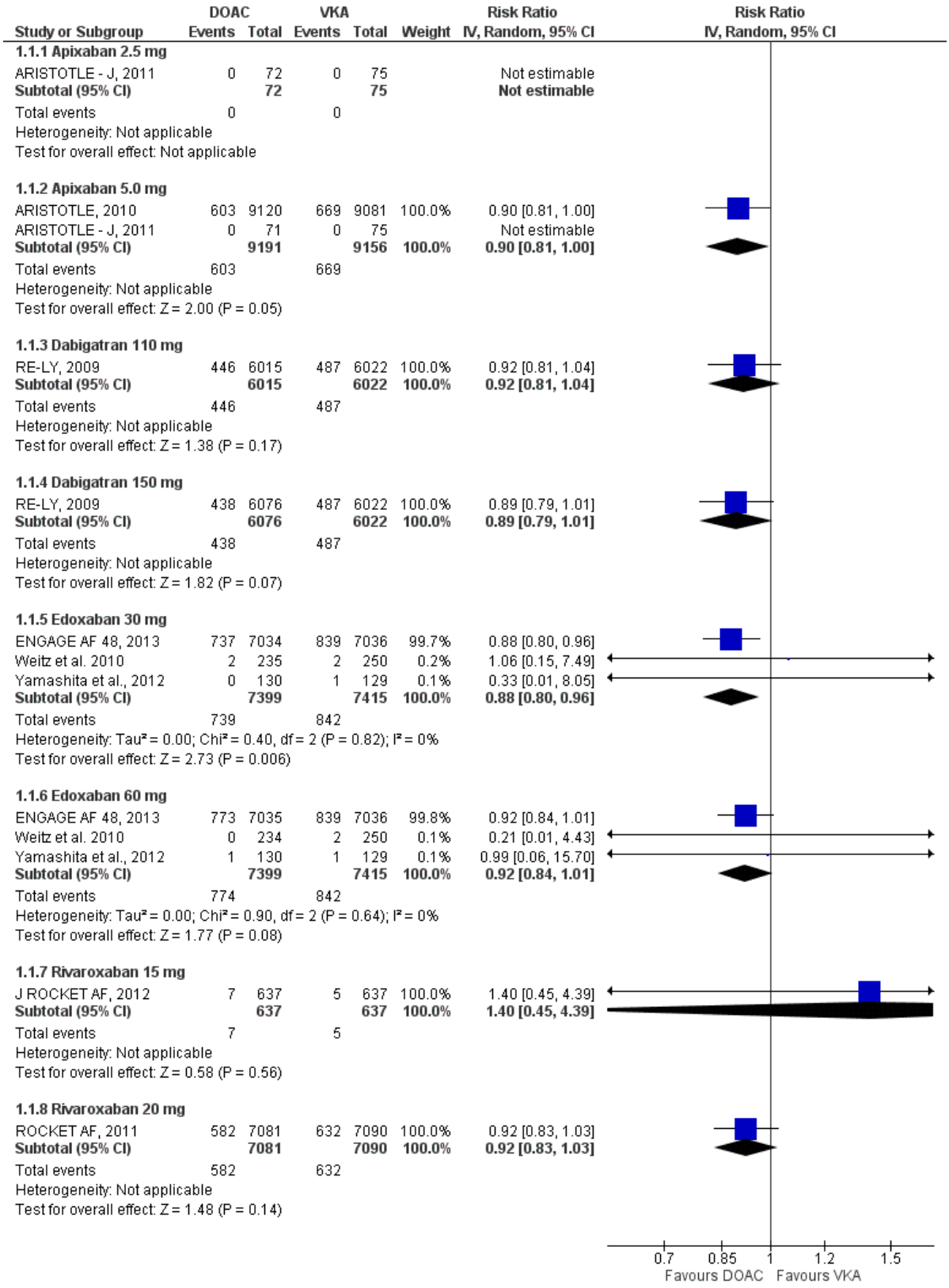
7.2.4 Clinical results

7.2.4.1 All-cause mortality: RCT evidence

For all-cause mortality, apixaban 5 mg twice daily and edoxaban 30 mg once daily showed statistically significant improvements compared to warfarin, translating to 7 fewer per 1,000 (from 13 fewer to 0 fewer; low certainty evidence) and 14 fewer per 1,000 (from 23 fewer to 5 fewer; moderate certainty evidence) (***Figure 2***). Other dosages and medications showed similar outcomes to warfarin, with dabigatran 150 mg twice daily (moderate certainty evidence) and edoxaban 60 mg once daily (moderate certainty evidence) reported as non-significant differences favouring DOACs. Rivaroxaban 15 mg showed inconclusive results, owing to the small event numbers leading to an imprecise effect estimate.

It should be noted that the ARISTOTLE-J study,[76] Weitz et al 2010[84] and Yamashita et al 2012[85] reported outcomes at 3 months while all other studies reported outcomes from 22–34 months. Evaluating the <12-month results separately changes the interpretation of the results for edoxaban 30 mg, which instead report no significant difference in all-cause mortality at <12 months (RR 0.77, 95% CI 0.15 to 4.09). Most analyses included only a single study with estimable results, so heterogeneity was not calculable. For analyses with more than 2 studies with estimable results, there was no evidence of heterogeneity.

Figure 2 All-cause mortality (RCTs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **IV**: inverse variance; **VKA:** vitamin-K antagonist.

Notes:

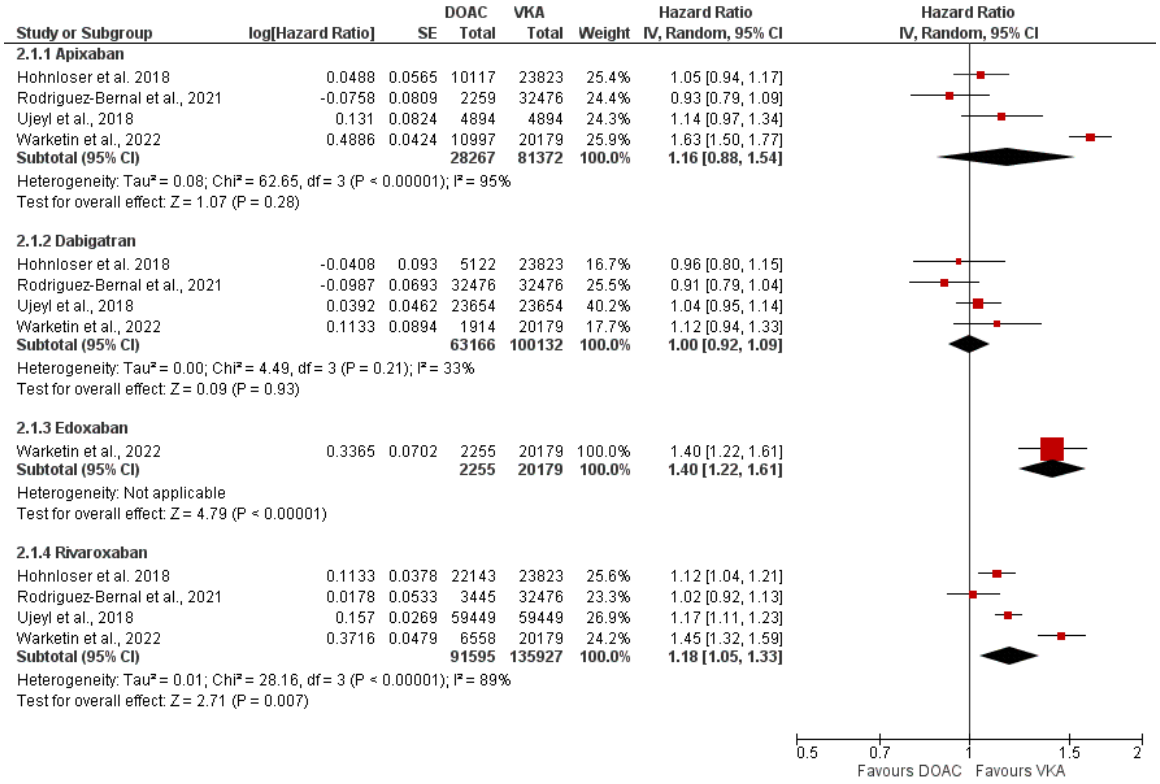
Warfarin was the VKA used in all included trials.

7.2.4.2 All-cause mortality: NRSI evidence

The NRSI evidence reporting HRs reported different results compared to the RCT evidence (***Figure 3***). There were no statistically significant differences reported for apixaban (very low certainty evidence) or dabigatran (moderate certainty evidence); however, there was a statistically significant increase in the risk of all-cause mortality for patients treated with edoxaban (low certainty evidence) and rivaroxaban (low certainty evidence). Moderate to considerable heterogeneity was reported for all analyses with more than 2 studies. As event rates were not clearly reported in the included studies, the absolute risks associated with the relative estimates are unknown.

A single NRSI that reported event rates (***Figure 4***) reported statistically significant reduction in all-cause mortality for dabigatran (20 fewer per 1,000, from 34 fewer to 2 fewer; very low certainty evidence). No statistically significant differences were reported for apixaban (very low certainty evidence) and rivaroxaban (very low certainty evidence). Substantial to considerable heterogeneity was reported for all analyses. It should be noted that Rodriguez-Bernal et al 2021, Korenstra et al 2016 and Hohnloser et al 2018 reported unmatched, unadjusted RR analyses, and are thus subject to a very high risk of confounding.[90,91,96]

Figure 3 All-cause mortality reported using HR (NRSIs)



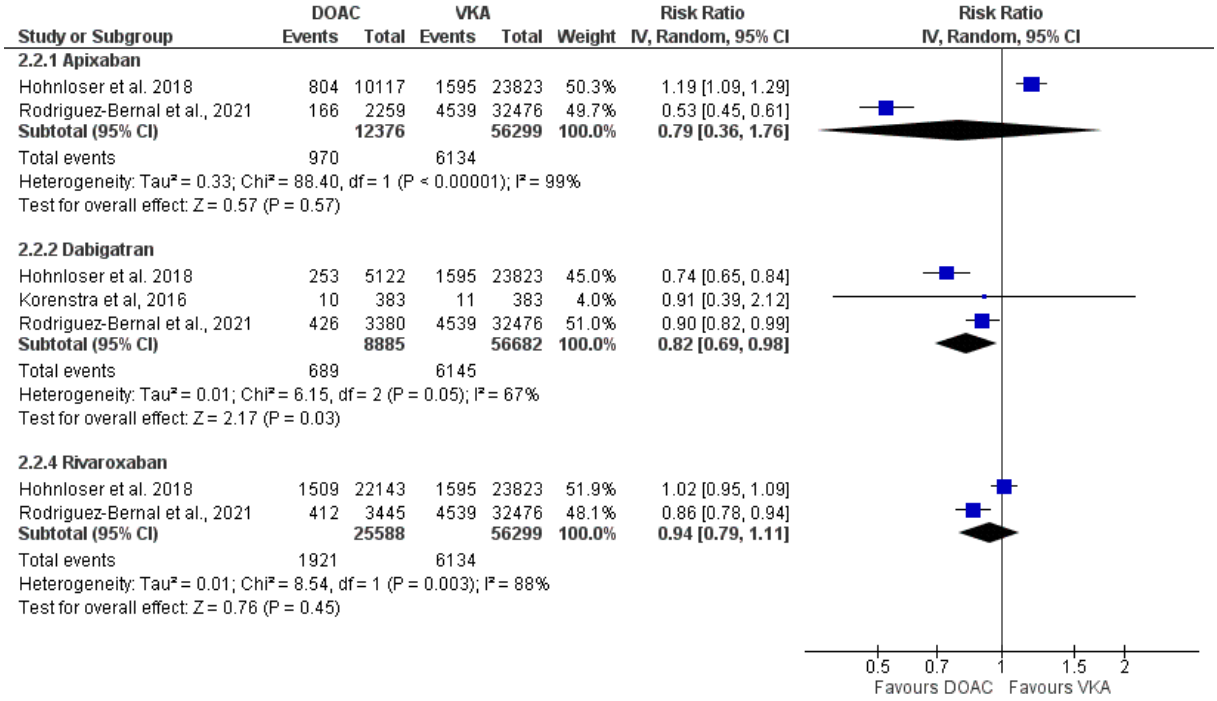
Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **IV**: inverse variance; **SE:** standard error; **VKA:** vitamin-K antagonist.

Notes

VKA used in all included trials was limited to acenocoumarol and phenprocoumon.

Figure 4 All-cause mortality reported using RR (NRSIs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

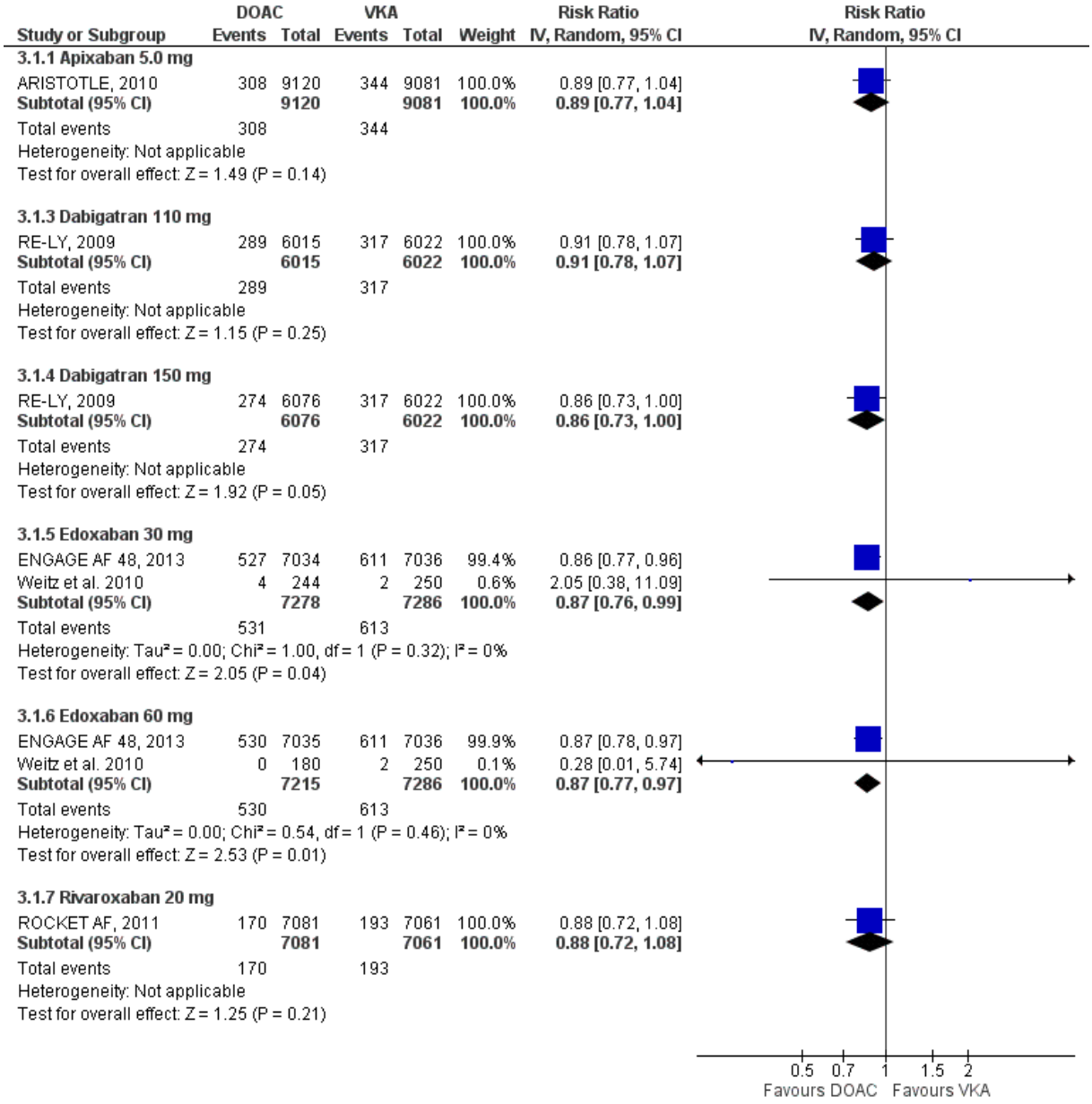
VKA used in all included trials was limited to acenocoumarol and phenprocoumon.

Trials did not report intervention doses.

7.2.4.3 Cardiovascular-related mortality: RCT evidence

For cardiovascular-related mortality, the direction of treatment effects broadly favoured DOACs. Edoxaban (30 mg and 60 mg once daily) showed statistically fewer cardiovascular-related deaths compared to warfarin, translating to a reduced risk of 11 fewer per 1,000 (from 20 fewer to 1 fewer; high certainty evidence) and 11 fewer per 1,000 (19 fewer to 3 fewer; high certainty evidence), respectively (***Figure 5***). Other DOACs showed non-statistically significant differences compared to warfarin (low to high certainty evidence). There was no evidence of heterogeneity in the meta-analyses.

Figure 5 Cardiovascular-related mortality (RCTs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **IV**: inverse variance; **VKA:** vitamin-K antagonist.

Notes:

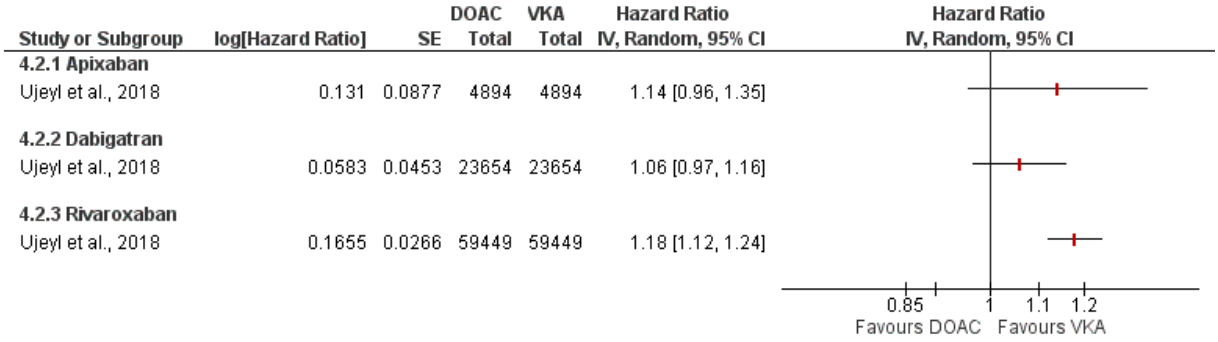
Warfarin was the VKA used in all included trials.

7.2.4.4 Cardiovascular-related mortality: NRSI evidence

One NRSI reported cardiovascular mortality using HRs (***Figure 6***), finding rivaroxaban to significantly increase the risk of cardiovascular-related mortality compared to VKAs (very low certainty evidence). There were no significant differences reported for apixaban or dabigatran (very low certainty evidence).

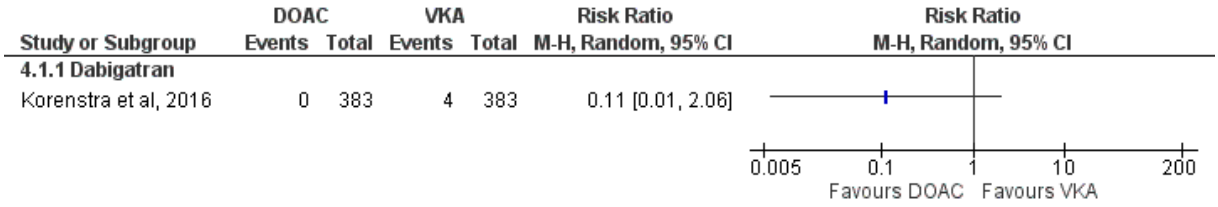
Similarly, the single study that reported cardiovascular mortality using RRs (***Figure 7***) found no significant difference for dabigatran. It should be noted that Korenstra et al 2016 reported unmatched, unadjusted RR analyses, so this study is subject to a very high risk of confounding.[90]

Figure 6 Cardiovascular-related mortality reported using HR (NRSI)



Abbreviations:
CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.
Notes:
VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

Figure 7 Cardiovascular-related mortality reported using RR (NRSI)



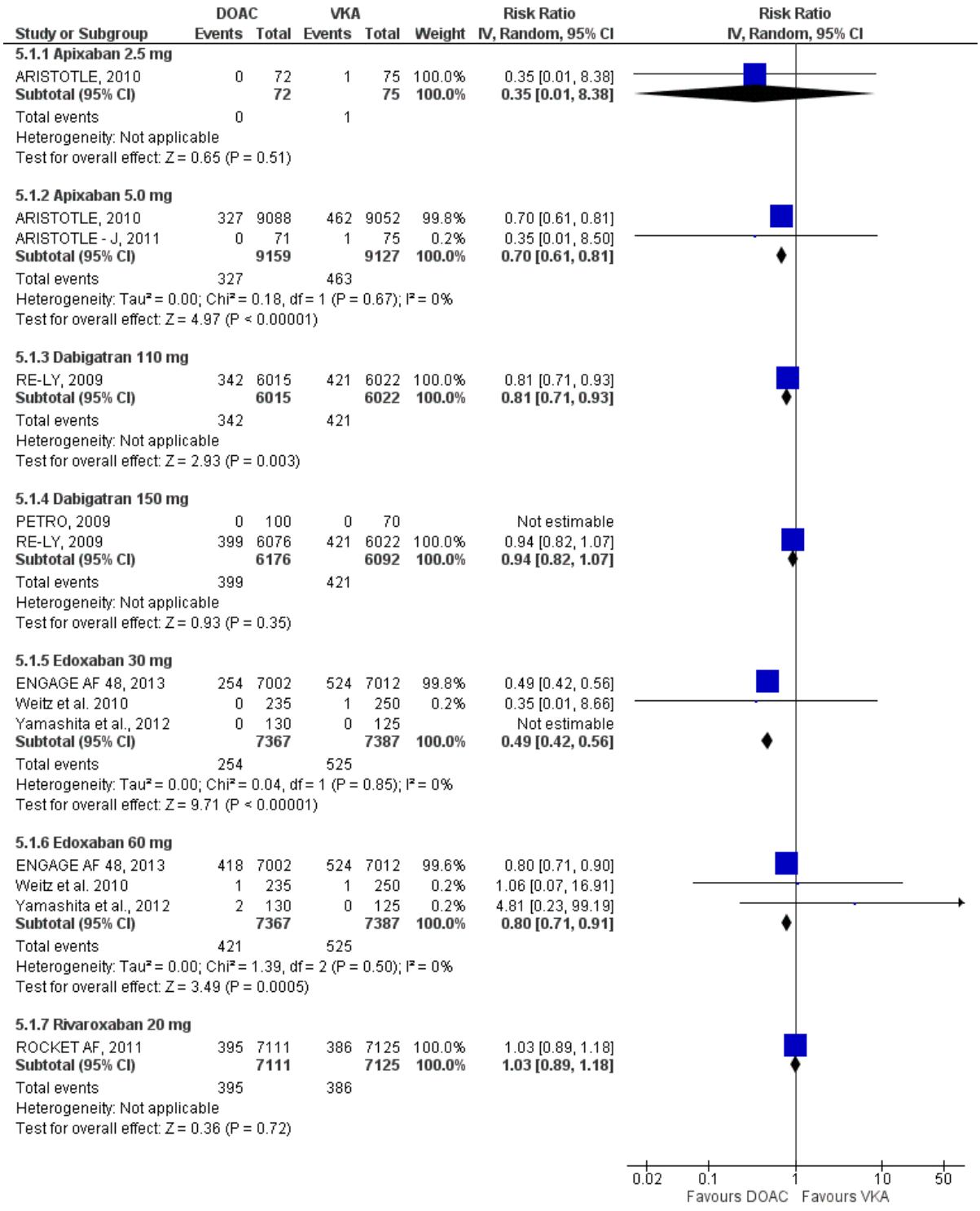
Abbreviations:
CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.
Notes:
VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

7.2.4.5 Major/life-threatening bleeding: RCT evidence

There was a statistically significant reduction in major/life-threatening bleeding for apixaban 5 mg twice daily (15 fewer per 1,000, from 20 fewer to 10 fewer; low certainty evidence), dabigatran 110 mg twice daily (13 fewer per 1,000, from 20 fewer to 5 fewer; moderate certainty evidence), edoxaban 30 mg once daily (36 fewer per 1,000, from 41 fewer to 31 fewer; moderate certainty evidence) and edoxaban 60 mg once daily (14 fewer per 1,000, from 21 fewer to 6 fewer; moderate certainty evidence) (***Figure 8***). Other doses and DOAC medications did not report statistically significant differences to warfarin for this outcome (very low certainty to high certainty evidence).

Separating out the results for <12 months changes the interpretation of the results slightly for edoxaban 30 mg and 60 mg, which show no statistically significant differences in major/life-threatening bleeding at <12 months (60 mg RR 4.81, 95% CI 0.23 to 99.19).

Figure 8 Major/life-threatening bleeding (RCTs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

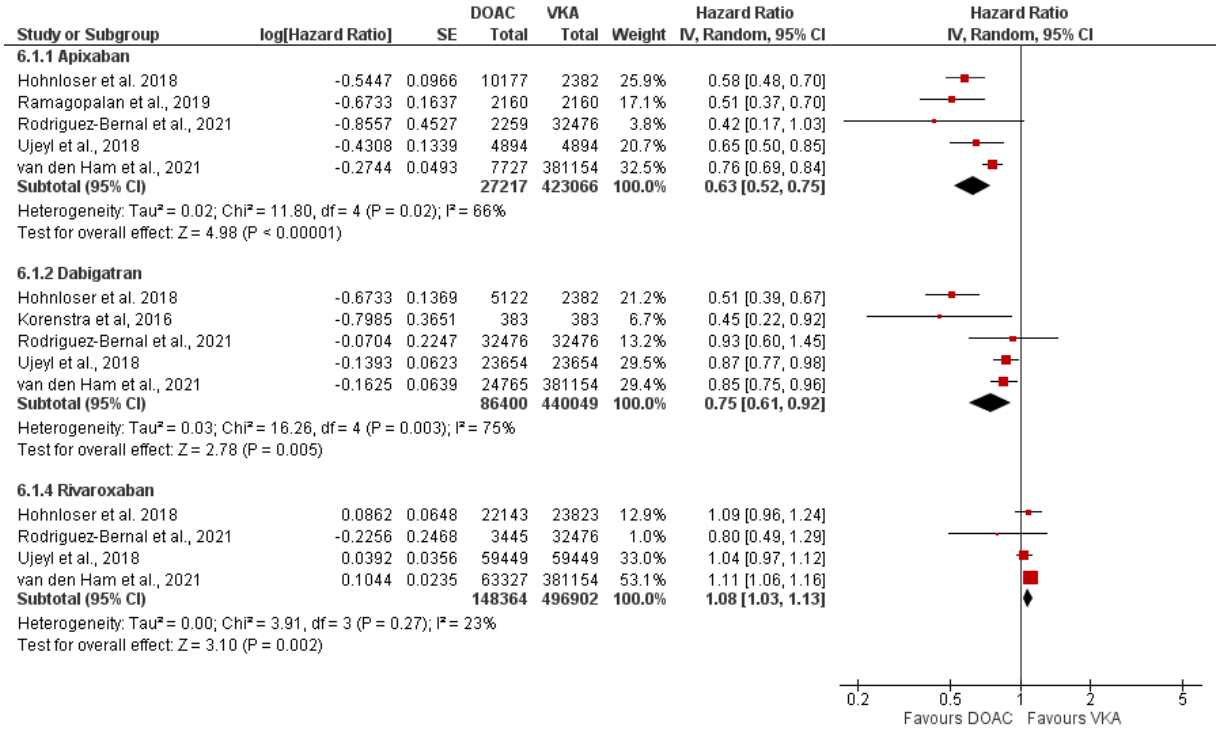
Warfarin was the VKA used in all included trials.

7.2.4.6 Major/life-threatening bleeding: NRSI evidence

Compared to VKAs, the NRSI analyses reporting HRs showed statistically significant reductions in major/life-threatening bleeding for apixaban (moderate certainty evidence) and dabigatran (moderate certainty evidence), and a statistically significant increase for rivaroxaban (moderate certainty evidence) (***Figure 9***). There was evidence of low heterogeneity in the rivaroxaban meta-analysis, moderate heterogeneity in the apixaban meta-analysis, and considerable heterogeneity in the dabigatran meta-analysis. As event rates were not reported in the included studies that reported HRs, the absolute risks associated with the relative estimates are unknown.

The NRSI analysis of RRs was in accordance with the HR analysis regarding apixaban (***Figure 10***), reporting a statistically significant reduction (8 fewer per 1,000, from 10 fewer to 6 fewer; very low certainty evidence), and dabigatran (6 fewer per 1,000, from 10 fewer to 1 fewer; very low certainty evidence). In contrast, rivaroxaban resulted in no statistically significant difference compared to VKAs (very low certainty evidence). There was evidence of low heterogeneity in the apixaban and rivaroxaban meta-analyses, and moderate heterogeneity in the dabigatran analysis. It should be noted that Rodriguez-Bernal et al 2021, Korenstra et al 2016, the RE-SONANCE study and Hohnloser et al 2018 reported unmatched, unadjusted RR analyses, and are thus subject to a very high risk of confounding.[88,90,91,96]

Figure 9 Major/life-threating bleeding reported using HR (NRSIs)



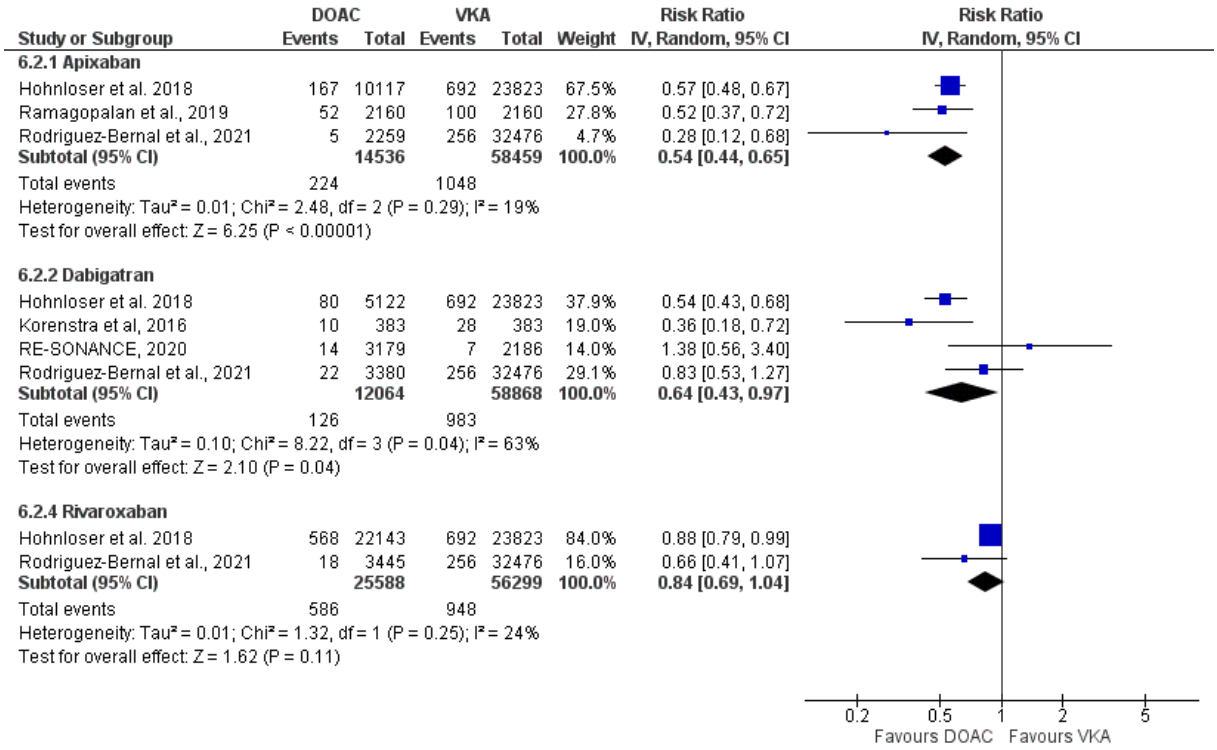
Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

Figure 10 Major/life-threating bleeding reported using RR (NRSIs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

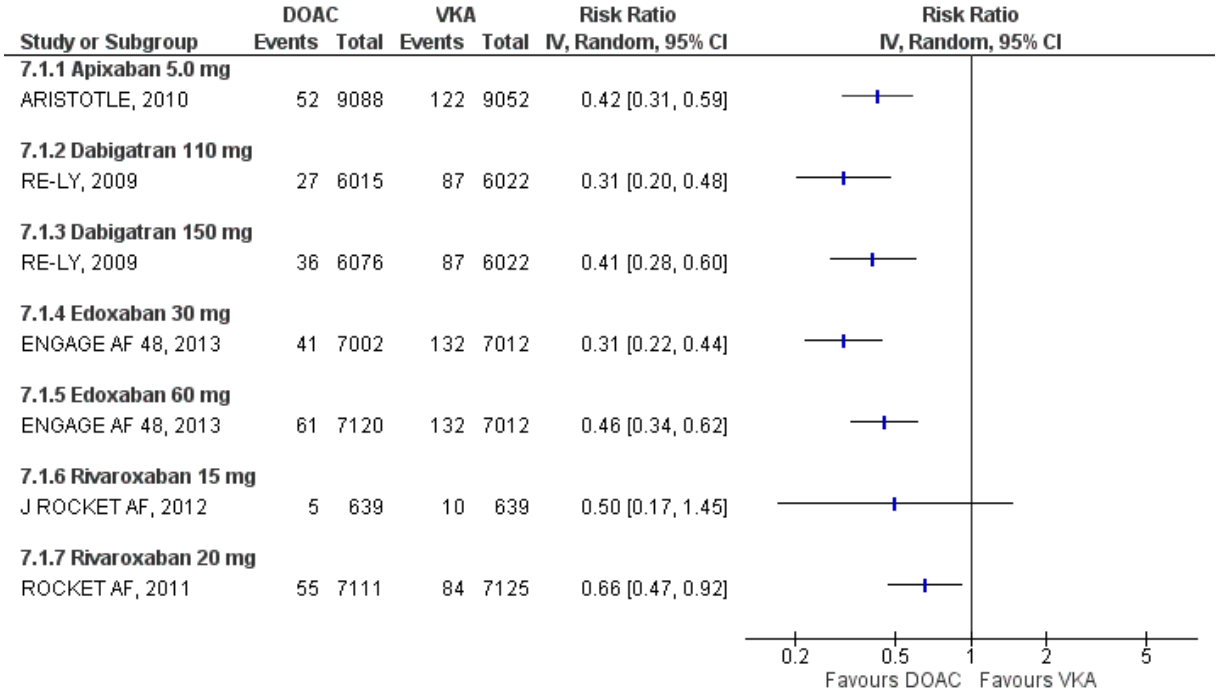
7.2.4.7 Intracranial bleeding: RCT evidence

The risk for intracranial bleeding was statistically significantly lower with DOACs compared to warfarin, except for rivaroxaban 15 mg once daily (***Figure 11***). Individual DOACs showed the following results:

- Apixaban 5 mg twice daily, 8 fewer per 1,000 (from 9 fewer to 6 fewer), low certainty evidence.
- Dabigatran 110 mg twice daily, 10 fewer per 1,000 (from 12 fewer to 8 fewer), moderate certainty evidence.
- Dabigatran 150 mg twice daily, 9 fewer per 1,000 (from 10 fewer to 6 fewer), moderate certainty evidence.
- Edoxaban 30 mg once daily, 13 fewer per 1,000 (from 15 fewer to 11 fewer), high certainty evidence.
- Edoxaban 60 mg once daily, 10 fewer per 1,000 (from 12 fewer to 7 fewer), high certainty evidence.
- Rivaroxaban 20 mg once daily, 4 fewer per 1,000 (6 fewer to 1 fewer), low certainty evidence.

Heterogeneity was not explored as meta-analysis was not conducted.

Figure 11 Intracranial bleeding (RCTs)



Abbreviations:
CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.
Notes:
Warfarin was the VKA used in all included trials.

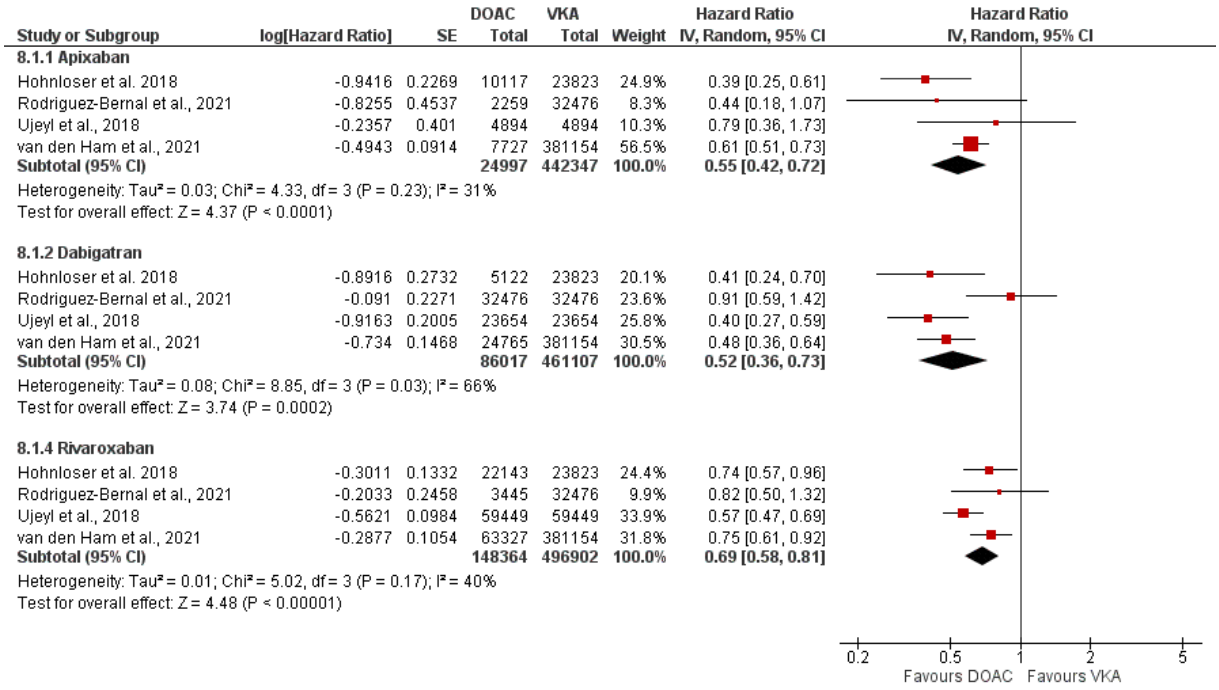
7.2.4.8 Intracranial bleeding: NRSI evidence

For the HR analysis (***Figure 12***), intracranial bleeding was statistically significantly reduced for apixaban (moderate certainty evidence), dabigatran (moderate certainty evidence) and rivaroxaban (moderate certainty evidence). As event rates were not reported in the included studies that reported HRs, the absolute risks associated with the relative estimates are unknown. For the RR analysis (***Figure 13***), intracranial bleeding was statistically significantly reduced for apixaban (6 fewer per 1,000, from 7 fewer to 4 fewer; very low certainty evidence), and rivaroxaban (5 fewer per 1,000, from 6 fewer to 2 fewer; very low certainty evidence).

The results for dabigatran were conflicting. The HR analysis was in favour of dabigatran, and the RR results reported no difference (HR: moderate certainty; RR: very low certainty evidence). There was high statistical heterogeneity in the dabigatran analysis, moderate heterogeneity in the rivaroxaban analysis, and no heterogeneity in the apixaban analysis.

It should be noted that Rodriguez-Bernal et al 2021, Korenstra et al 2016 and Hohnloser et al 2018 reported unmatched, unadjusted RR analyses, and are thus subject to a very high risk of confounding.[90,91,96]

Figure 12 Intracranial bleeding reported using HR (NRSIs)



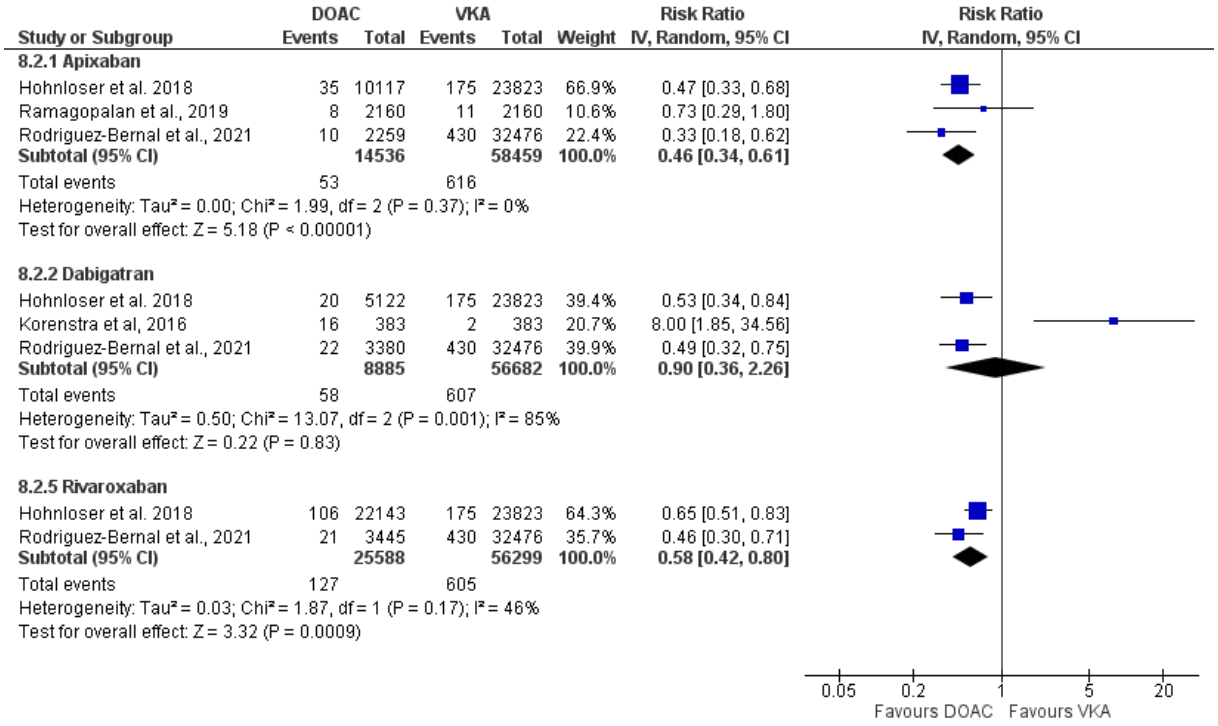
Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes

VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

Figure 13 Intracranial bleeding reported using RR (NRSIs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

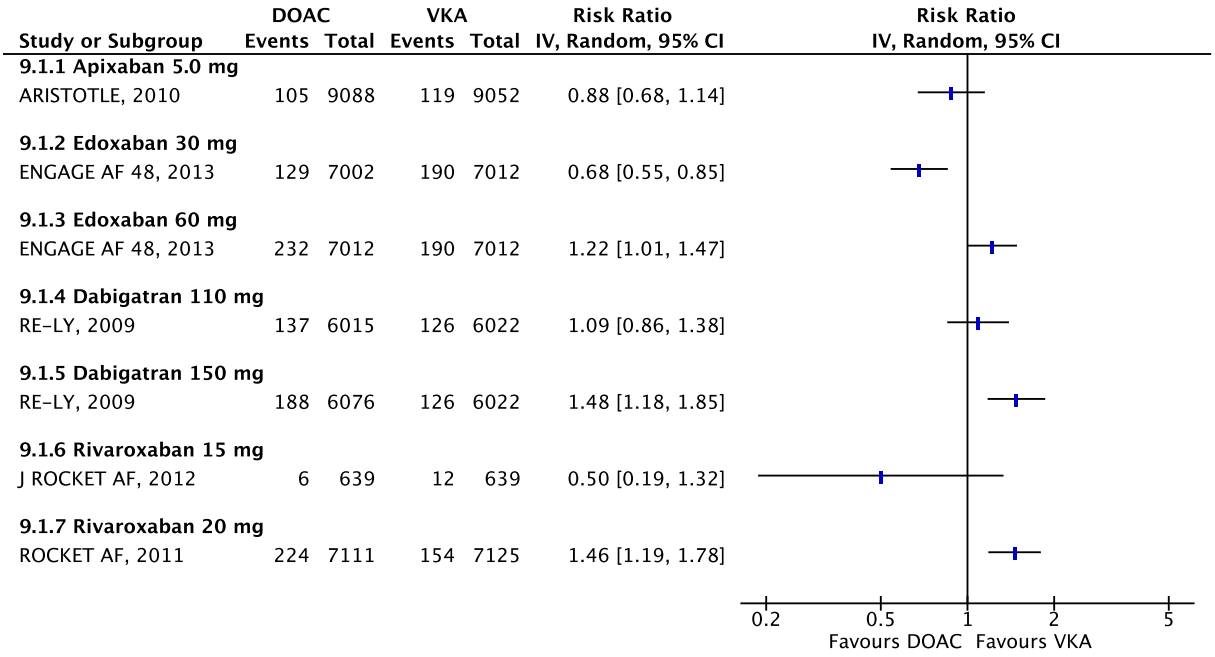
Notes:

VKA used in all included trials was limited to acenocoumarol and phenprocoumon trials did not report intervention doses.

7.2.4.9 Gastrointestinal bleeding: RCT evidence

Where reported, the impact of the DOACs on GI bleeding compared to warfarin was varied (***Figure 14***). Apixaban 5 mg twice daily (low certainty evidence), dabigatran 110 mg twice daily (moderate certainty evidence), and rivaroxaban 15 mg once daily showed no statistically significant difference in GI bleeding compared to warfarin (low certainty evidence). Dabigatran 150 mg twice daily showed a statistically significantly increase in bleeding events (10 more per 1,000, from 4 more to 18 more; moderate certainty evidence). Edoxaban 30 mg once daily showed a statistically significant lower risk in GI bleeding events (9 fewer per 1,000, from 12 fewer to 4 fewer; high certainty evidence), and edoxaban 60 mg once daily showed a statistically significantly increase in bleeding events (6 more per 1,000, from 0 fewer to 13 more; high certainty evidence). Finally, rivaroxaban 20 mg once daily, showed a statistically significant increase in GI bleeding (10 more per 1,000, from 4 more to 17 more; high certainty evidence). Heterogeneity was not evaluated as meta-analyses were not conducted.

Figure 14 Gastrointestinal bleeding (RCTs)



Abbreviations

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

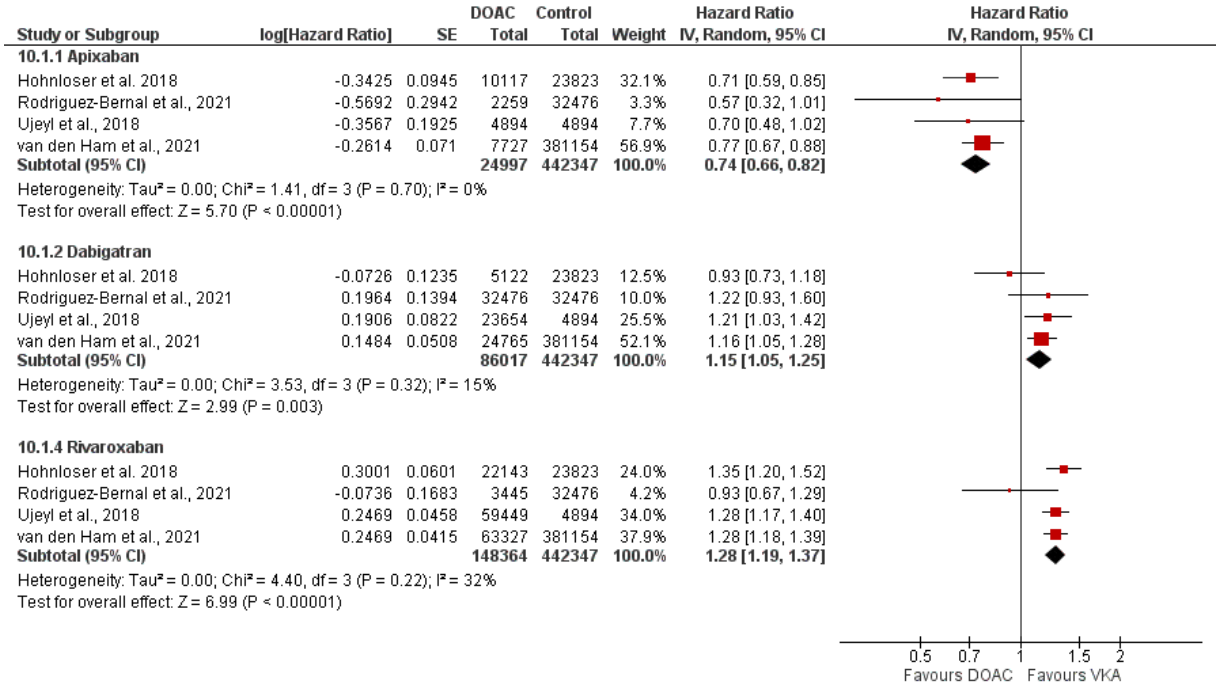
Warfarin was the VKA used in all included trials.

7.2.4.10 Gastrointestinal bleeding: NRSI evidence

GI bleeding was statistically significantly reduced for apixaban in the HR analysis (moderate certainty evidence) and the RR analysis (26 fewer per 1,000, from 32 fewer to 0 fewer; very low certainty evidence) (***Figure 15***, ***Figure 16***). The results for dabigatran were conflicting between the HR (significantly favouring VKA; moderate certainty evidence) and RR (no statistical difference; very low certainty evidence) analyses; similarly, the results for rivaroxaban were conflicting between the HR (significantly favouring VKAs; moderate certainty evidence) and RR (no statistical difference; very low certainty evidence) analysis. There was moderate statistical heterogeneity in the rivaroxaban HR results, but none for the other HR comparisons. There was considerable heterogeneity in the apixaban and rivaroxaban RR results. Similarly, there was substantial heterogeneity in the dabigatran RR results.

It should be noted that Rodriguez-Bernal et al 2021, Korenstra et al 2016, the RE-SONANCE study and Hohnloser et al 2018 reported unmatched, unadjusted RR analyses, and are thus subject to a very high risk of confounding.[88,90,91,96]

Figure 15 Gastrointestinal bleeding reported using HR (NRSIs)



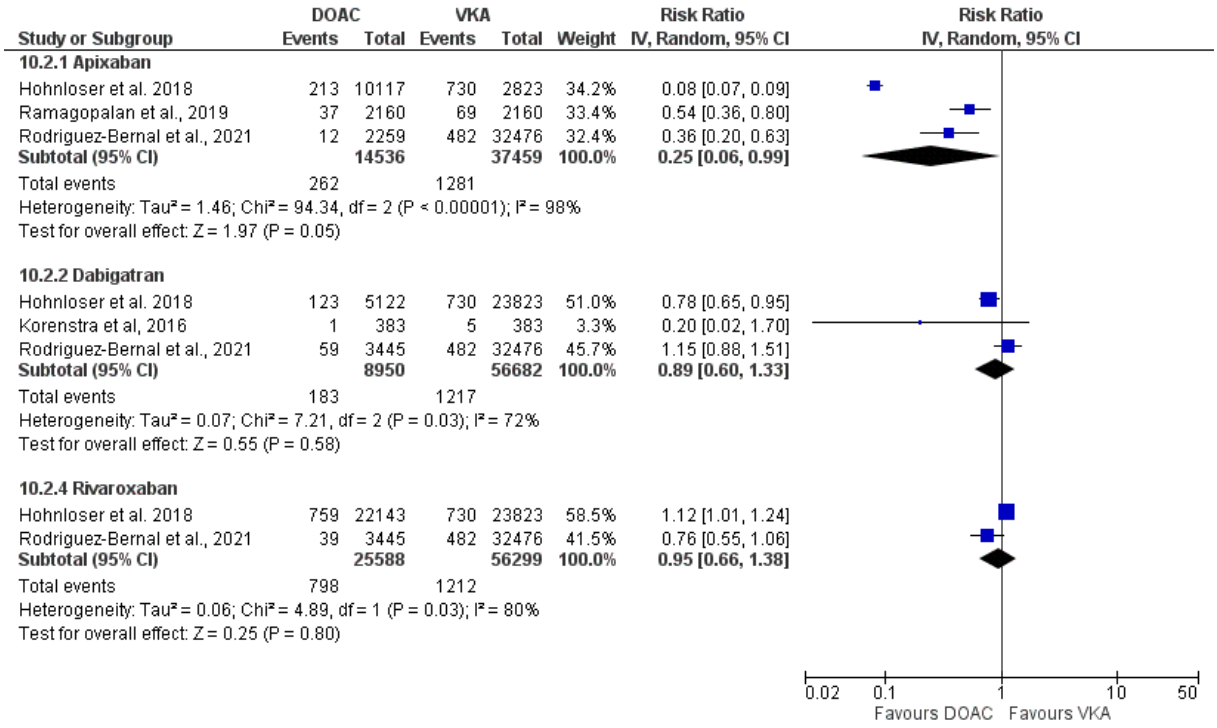
Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

Figure 16 Gastrointestinal bleeding reported using RR (NRSIs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

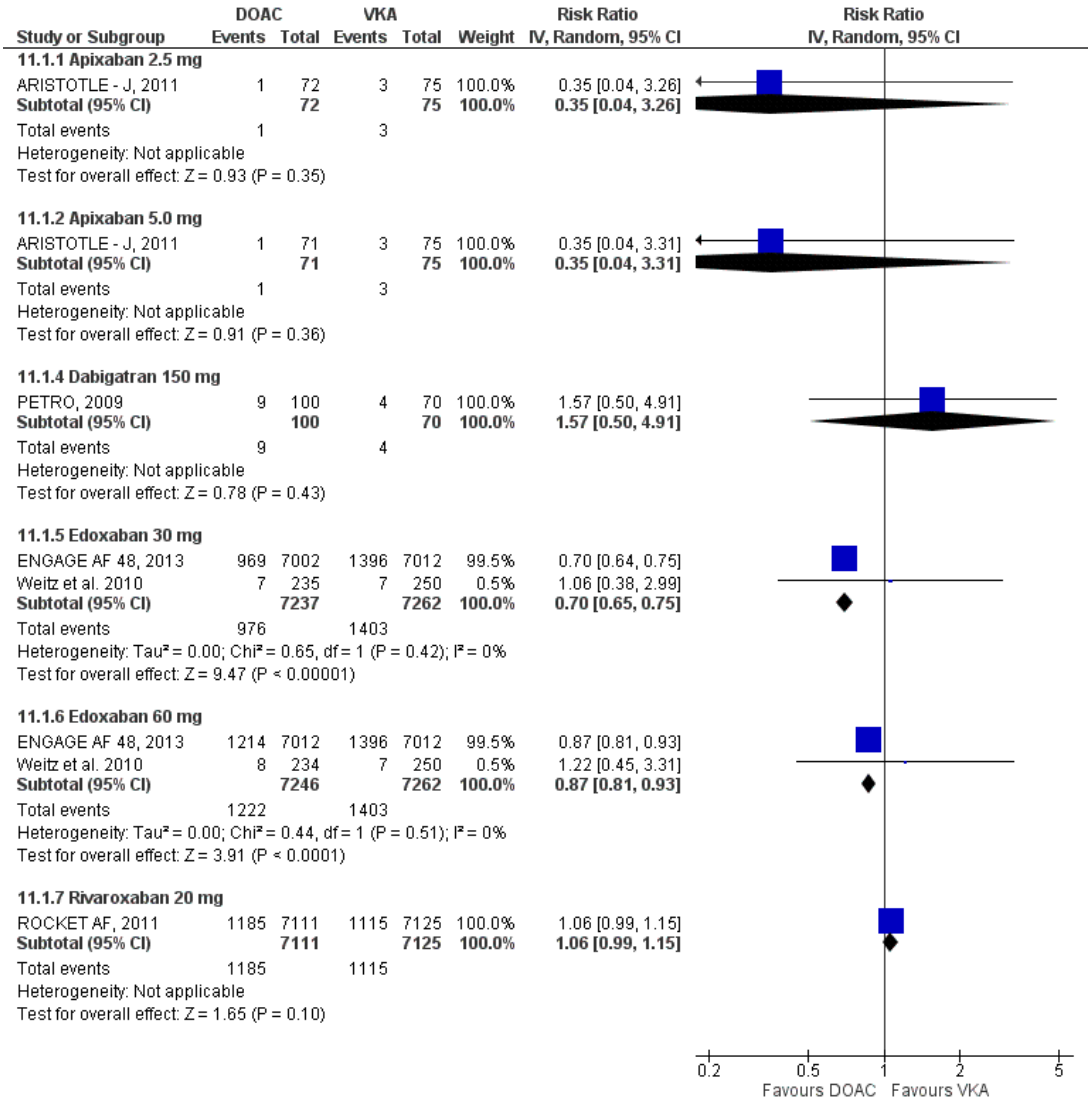
Notes

VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

7.2.4.11 Clinically-relevant bleeding: RCT evidence

Compared to warfarin, the meta-analysis reported a statistically significant reduction in the number of clinically-relevant bleeding events for patients treated with edoxaban 30 mg once daily (58 fewer per 1,000, from 68 fewer to 48 fewer; high certainty evidence) and edoxaban 60 mg once daily (25 fewer per 1,000, from 37 fewer to 14 fewer; high certainty evidence) (***Figure 17***). There was no evidence of heterogeneity in these meta-analyses. All other comparisons were reported by single trials. Apixaban 2.5 mg once daily (very low certainty evidence) or 5 mg once daily (very low certainty evidence) and dabigatran 150 mg twice daily (very low certainty evidence) and rivaroxaban 20 mg once daily (high certainty evidence) showed no statistically significant differences when compared to warfarin.

Figure 17 Clinically-relevant bleeding (RCTs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

Warfarin was the VKA used in all included trials.

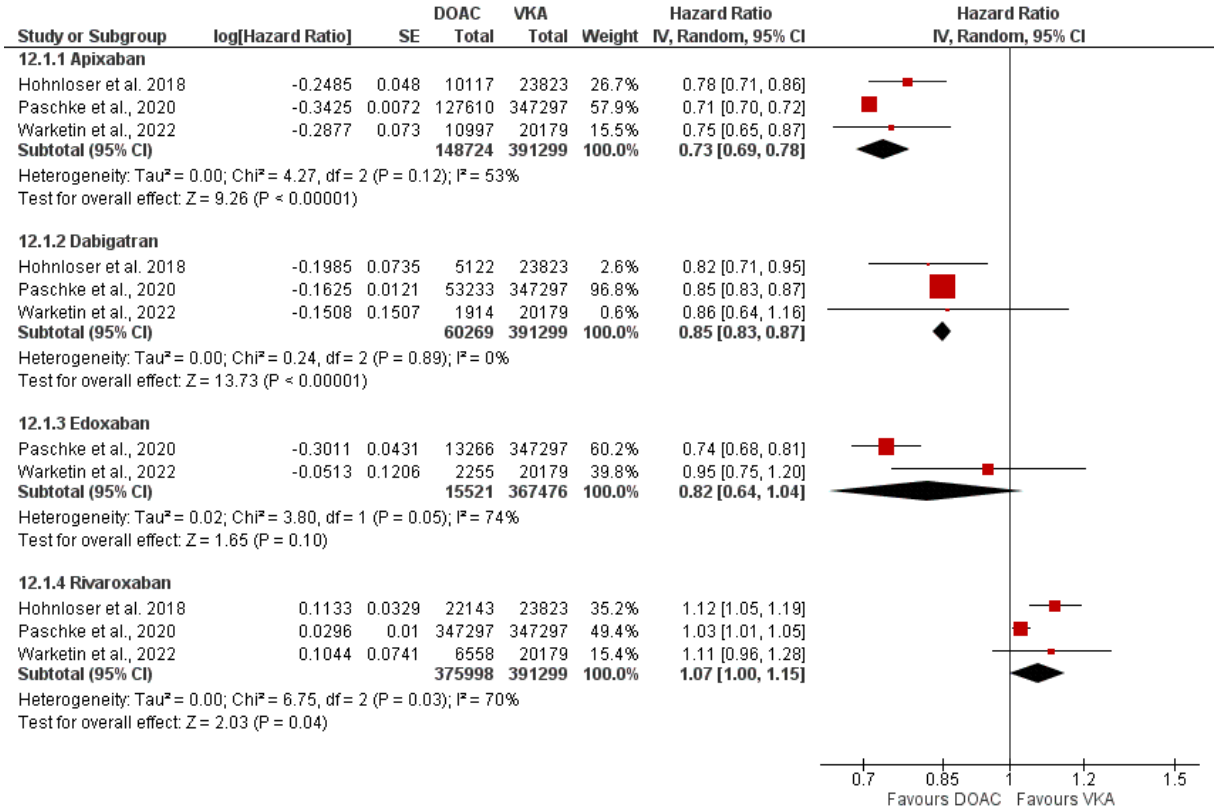
7.2.4.12 Clinically-relevant bleeding: NRSI evidence

Clinically-relevant bleeding was statistically significantly reduced for apixaban (low certainty evidence) and dabigatran (low certainty evidence), there was no difference for edoxaban (very low certainty evidence), and it was statistically significantly increased for rivaroxaban (low certainty evidence) (***Figure 18***). There was high heterogeneity in the edoxaban and rivaroxaban comparisons, but none in the other analyses. As event rates were not reported in the included studies reporting HRs, the absolute risks associated with the relative estimates are unknown.

In accordance with the HR analysis, the NRSI analysis of RRs (***Figure 19***) showed a statistically significant reduction for apixaban (27 fewer per 1,000, from 32 fewer to 21 fewer; low certainty evidence)

and dabigatran (31 fewer per 1,000, from 39 fewer to 23 fewer; low certainty evidence). There was no difference for rivaroxaban (low certainty evidence). Hohnloser et al 2018 reported unmatched, unadjusted RR analyses, which are thus subject to a very high risk of confounding.[96]

Figure 18 Clinically-relevant bleeding reported using HR (NRSIs)



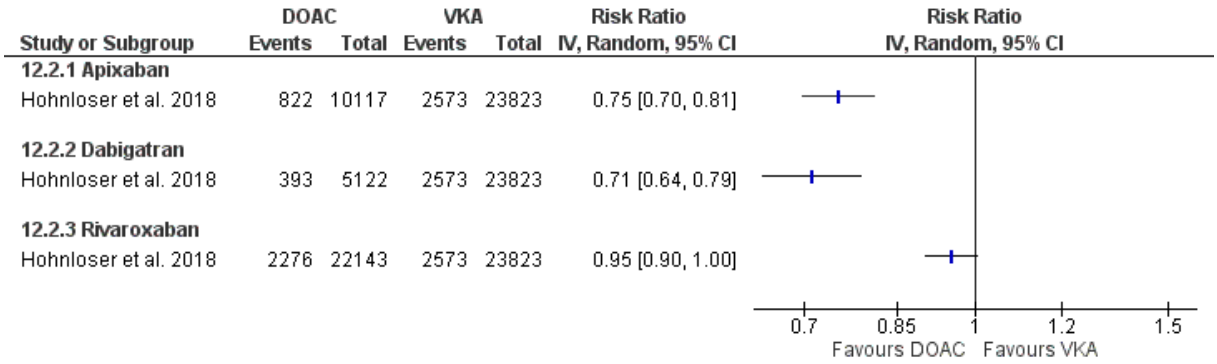
Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

Figure 19 Clinically-relevant bleeding reported using RR (NRSIs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

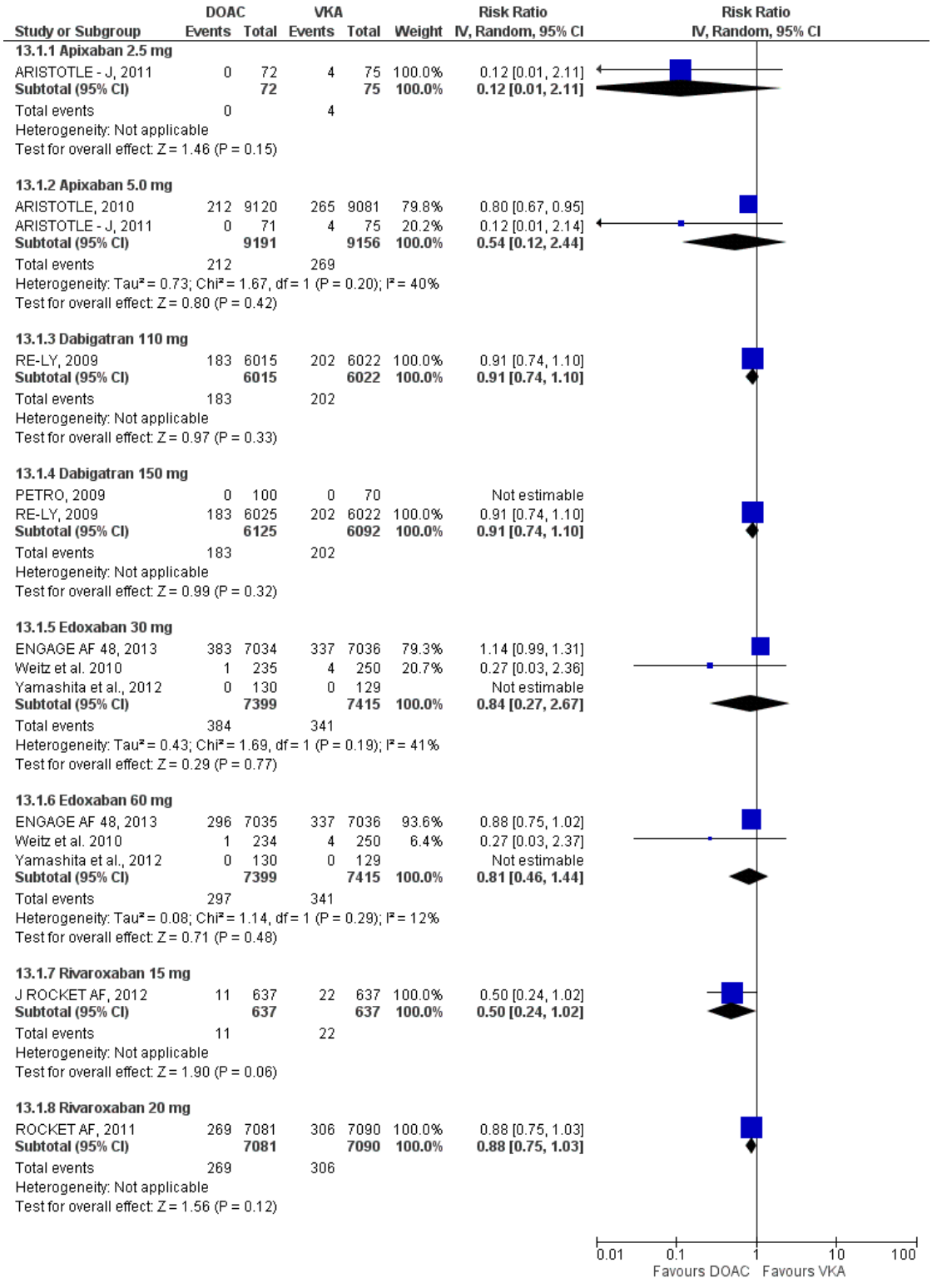
Notes

VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

7.2.4.13 Stroke or systemic embolic event: RCT evidence

Across all DOACs (type and dose) there were no statistically significant differences reported for all stroke or SE compared to warfarin (***Figure 20***). The meta-analyses reported low to moderate levels of heterogeneity, driven by small studies with large statistical imprecision. The certainty of the evidence for each outcome was very low (apixaban 2.5 mg twice daily, apixaban 5 mg twice daily, edoxaban 30 mg once daily), low (edoxaban 60 mg once daily, rivaroxaban 15 mg once daily), moderate (dabigatran 110 mg twice daily, dabigatran 150 mg twice daily) or high (rivaroxaban 20 mg once daily).

Figure 20 Stroke or systemic embolic event (RCTs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

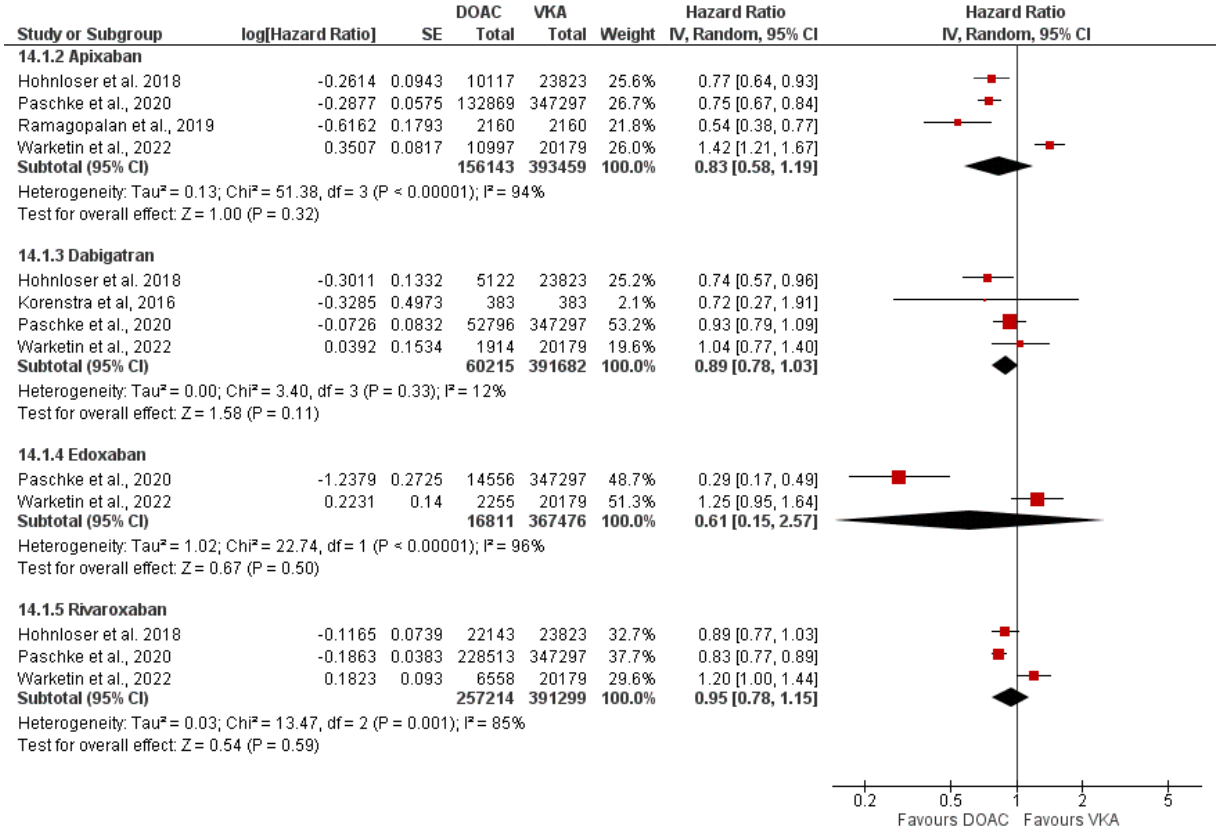
Warfarin was the VKA used in all included trials.

7.2.4.14 Stroke or systematic embolic event: NRSI evidence

Across all DOACs (type and dose) there was no statistically significant difference in total stroke and SE compared to phenprocoumon or acenocoumarol in the HR analyses (***Figure 21***); however, it is worth noting that the apixaban, edoxaban and rivaroxaban comparisons had considerable heterogeneity and the certainty of evidence for all comparisons was either very low or low. In the RR analysis (***Figure 22***), there were statistically significant reductions favouring dabigatran (5 fewer per 1,000, from 9 fewer to 0 fewer; very low certainty evidence) and rivaroxaban (5 fewer per 1,000, from 7 fewer to 2 fewer; very low certainty evidence), but no significant difference for apixaban (very low certainty evidence).

It should be noted that Korenstra et al 2016 and Hohnloser et al 2018 reported unmatched, unadjusted RR analyses, so is thus subject to a very high risk of confounding.[90,96]

Figure 21 Stroke or systemic embolic events reported using HR (NRSIs)



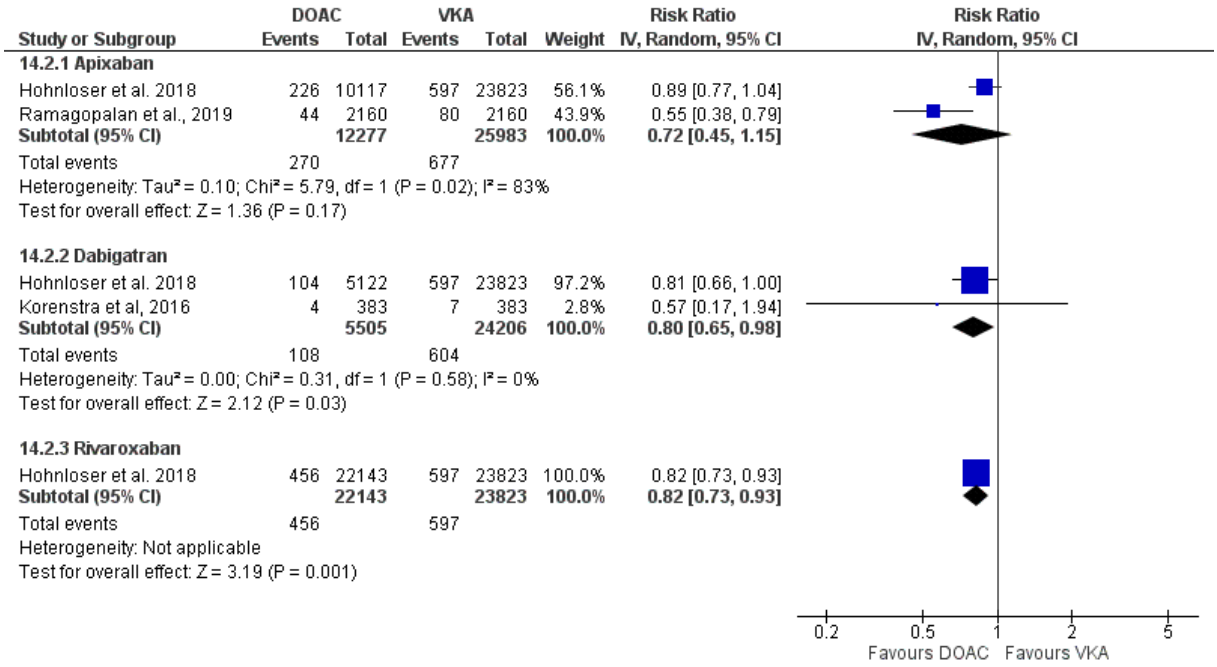
Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

Figure 22 Stroke or systemic embolic events reported using RR (NRSIs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist

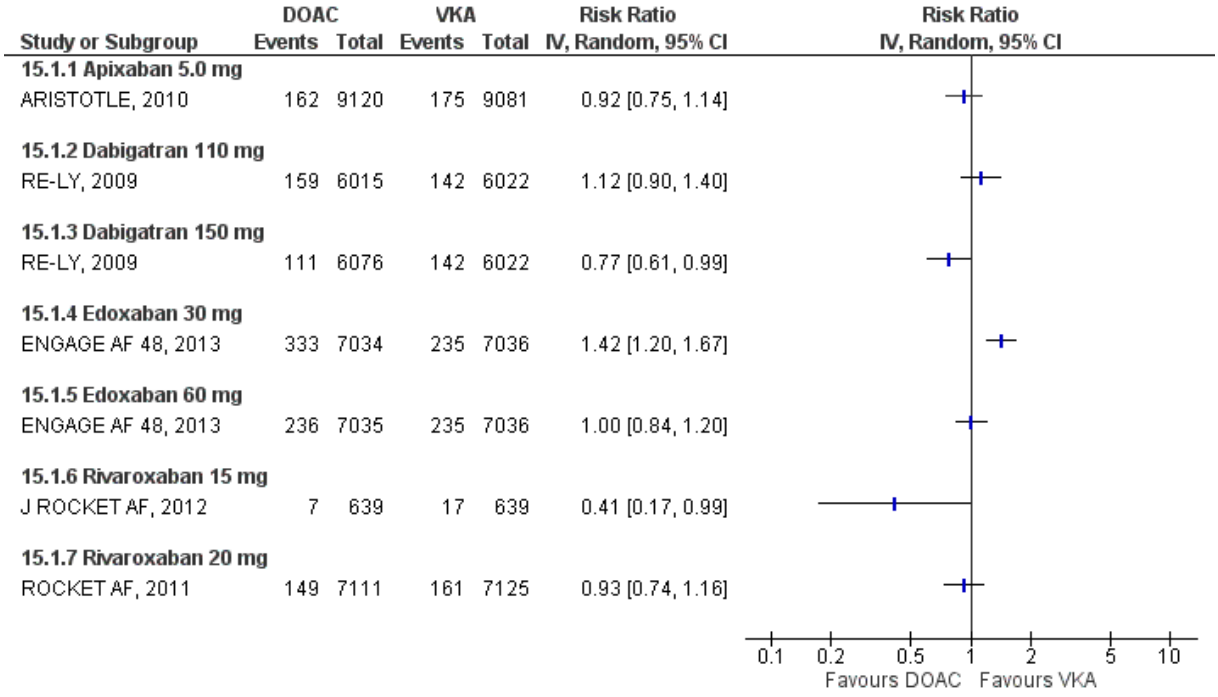
Notes:

VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

7.2.4.15 Ischaemic stroke: RCT evidence

The RCT results for ischaemic stroke found that apixaban 5 mg twice daily (low certainty evidence), dabigatran 110 mg twice daily (moderate certainty evidence), edoxaban 60 mg once daily (high certainty evidence) and rivaroxaban 20 mg (high certainty evidence) showed no statistically significant difference compared to warfarin (***Figure 23***). In contrast, dabigatran 150 mg twice daily and rivaroxaban 15 mg once daily showed statistically significant decreases in ischaemic stroke risk, translating to 5 fewer events per 1,000 patients (9 fewer to 0 fewer; moderate certainty evidence) and 16 fewer per 1,000 patients (22 fewer to 0 fewer; low certainty evidence), respectively. Edoxaban 30 mg once daily increased ischaemic stroke risk compared to warfarin, translating to 14 more per 1,000 patients (7 more to 25 more; high certainty evidence). Meta-analyses were not conducted, so heterogeneity was not assessed.

Figure 23 Ischaemic stroke (RCTs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

Warfarin was the VKA used in all included trials.

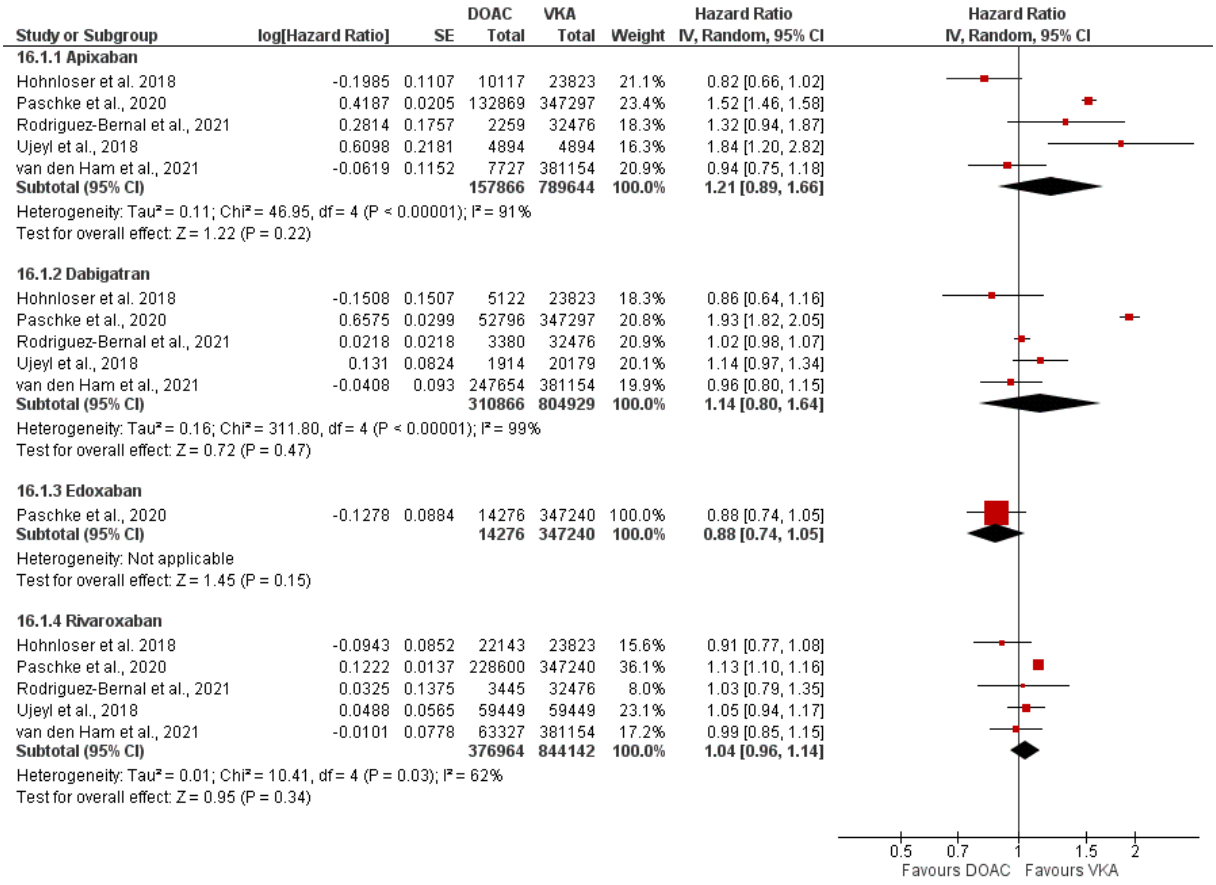
7.2.4.16 Ischaemic stroke: NRSI evidence

The meta-analyses of HRs indicated that apixaban, dabigatran, edoxaban and rivaroxaban showed no statistically significant increase in ischaemic stroke (very low certainty evidence) (***Figure 24***). The dabigatran and apixaban meta-analyses were subject to considerable heterogeneity. As event rates were not reported in the included studies that reported HRs, the absolute risks associated with the relative estimates are unknown.

In contrast, the RR analysis indicated that rivaroxaban was associated with a significant decrease in ischemic stroke of 2 fewer per 1,000 (form 4 fewer to 0 fewer; very low certainty evidence), apixaban resulted in a non-significant decrease in ischaemic stroke (very low certainty evidence), and dabigatran showed a non-significant increase in ischaemic stroke (very low certainty evidence) (***Figure 25***). The apixaban meta-analysis was subject to considerable heterogeneity.

It should be noted that Rodriguez-Bernal et al 2021, Korenstra et al 2016, the RE-SONANCE study and Hohnloser et al 2018, reported unmatched, unadjusted RR analyses, and are thus subject to a very high risk of confounding.[88,90,91,96]

Figure 24 Ischaemic stroke reported using HR (NRSIs)



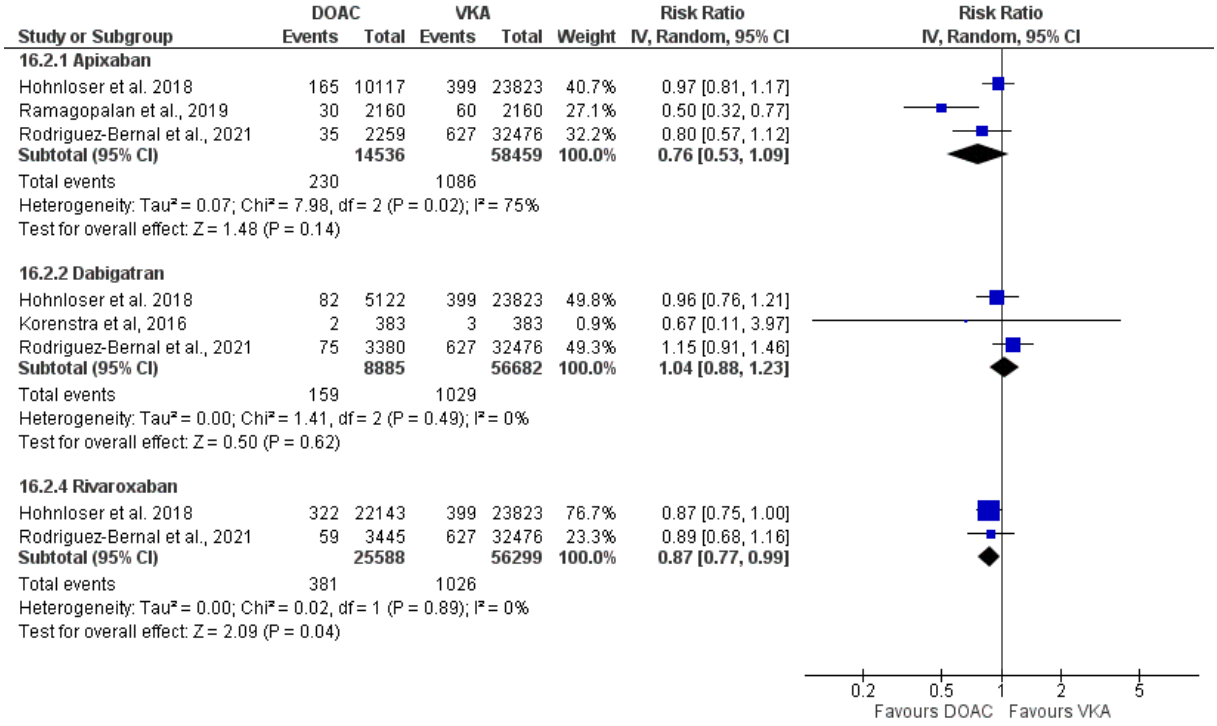
Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

Figure 25 Ischaemic stroke reported using RR (NRSIs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

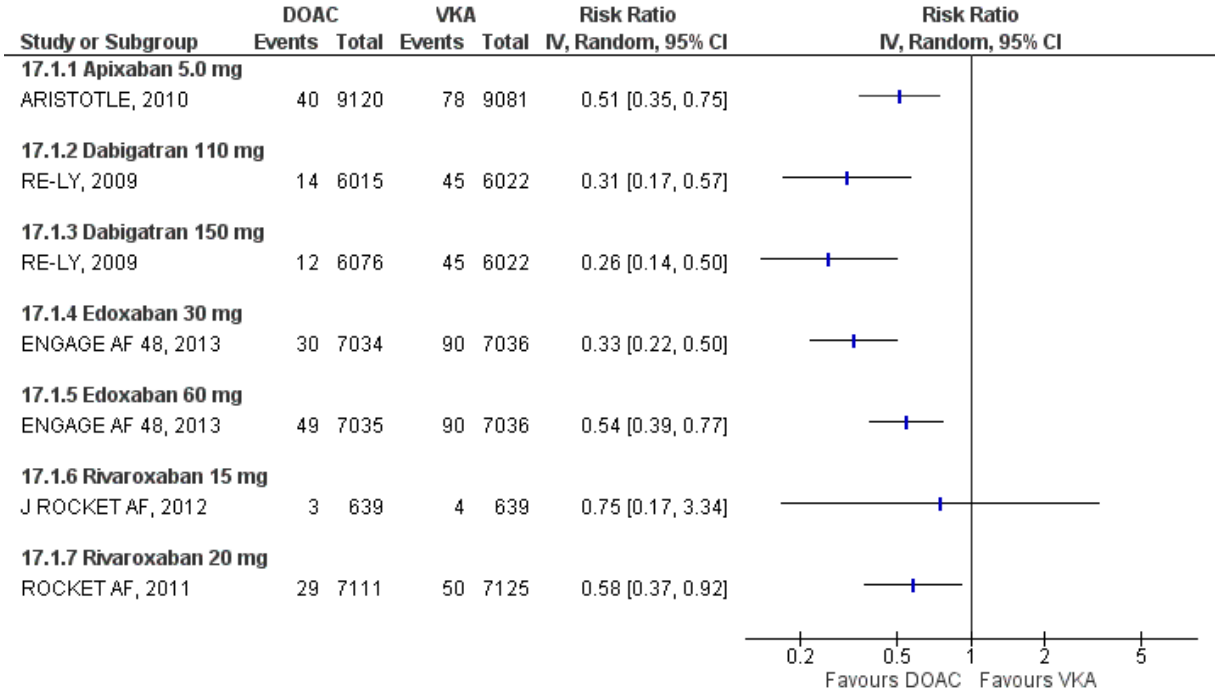
VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

7.2.4.17 Haemorrhagic stroke: RCT evidence

All DOACs showed a statistically significant reduction in the risk of haemorrhagic stroke, except for rivaroxaban 15 mg once daily (low certainty evidence). Results for the other DOACs are as follows (***Figure 26***):

- Apixaban 5 mg twice daily, 4 fewer per 1,000 (from 6 fewer to 2 fewer); moderate certainty evidence.
- Dabigatran 110 mg twice daily, 5 fewer per 1,000 (from 6 fewer to 3 fewer); moderate certainty evidence.
- Dabigatran 150 mg twice daily, 6 fewer per 1,000 (from 6 fewer to 4 fewer); moderate certainty evidence.
- Edoxaban 30 mg once daily, 9 fewer per 1,000 (from 10 fewer to 6 fewer); high certainty evidence.
- Edoxaban 60 mg once daily, 6 fewer per 1,000 (from 8 fewer to 3 fewer); high certainty evidence.
- Rivaroxaban 20 mg once daily, 3 fewer per 1,000 (from 4 fewer to 1 fewer); high certainty evidence.

Figure 26 Haemorrhagic stroke (RCTs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

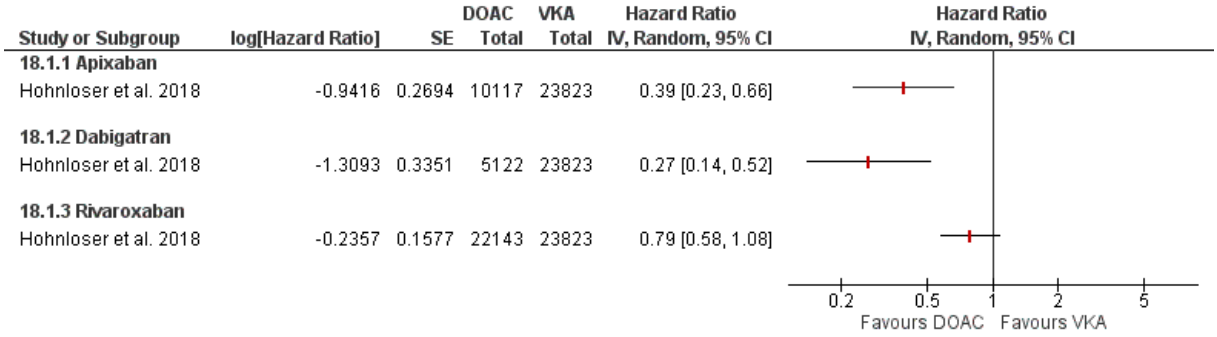
7.2.4.18 Haemorrhagic stroke: NRSI evidence

The meta-analyses of HRs indicated that apixaban (low certainty evidence) and dabigatran (low certainty evidence) were associated with a statistically significant decrease in haemorrhagic stroke, while rivaroxaban showed no statistically significant decrease in haemorrhagic stroke (low certainty evidence) (***Figure 27***). As event rates were not reported in the included study reporting HRs, the absolute risks associated with the relative estimates are unknown.

In contrast, the RR analysis indicated that apixaban (3 fewer per 1,000, from 3 fewer to 1 fewer; low certainty evidence), dabigatran (3 fewer per 1,000, from 4 fewer to 1 fewer; low certainty evidence) and rivaroxaban (1 fewer per 1,000, from 2 fewer to 0 fewer; low certainty evidence) were associated with a statistically significant decrease in haemorrhagic stroke (***Figure 28***).

It should be noted that Hohnloser et al 2018 reported unmatched, unadjusted RR analyses, thus is subject to a very high risk of confounding.[96]

Figure 27 Haemorrhagic stroke reported using HR (NRSIs)



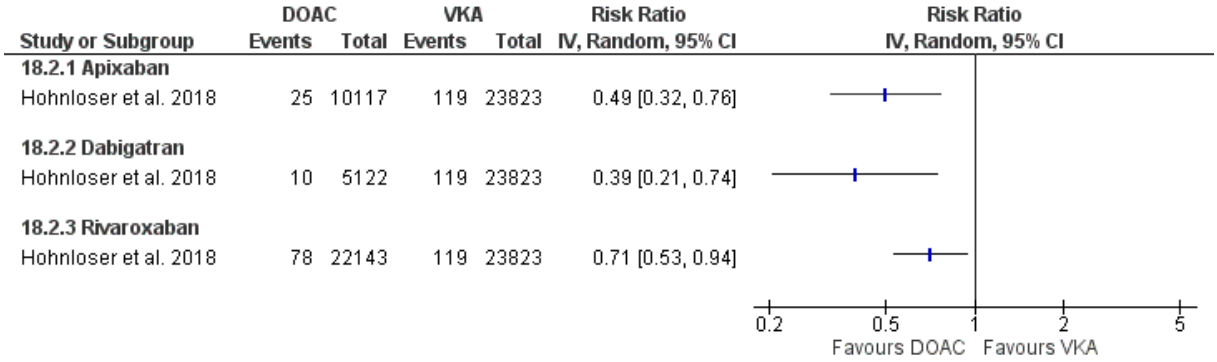
Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

Figure 28 Haemorrhagic stroke reported using RR (NRSIs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

7.2.4.19 Cognitive functioning: RCT evidence

None of the included RCTs reported cognitive function in NVAF patients.

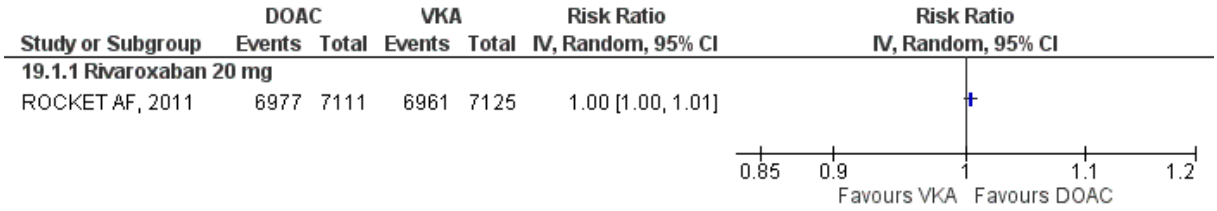
7.2.4.20 Cognitive functioning: NRSI evidence

None of the included NRSIs reported cognitive function in NVAF patients.

7.2.4.21 Adherence: RCT evidence

Only one RCT reported adherence to treatment plans. Rivaroxaban 20 mg once daily showed no significant difference in adherence compared to warfarin (high certainty evidence) (***Figure 29***).

Figure 29 Adherence (RCTs)



Abbreviations:
CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.
Notes:
Warfarin was the VKA used in all included trials.

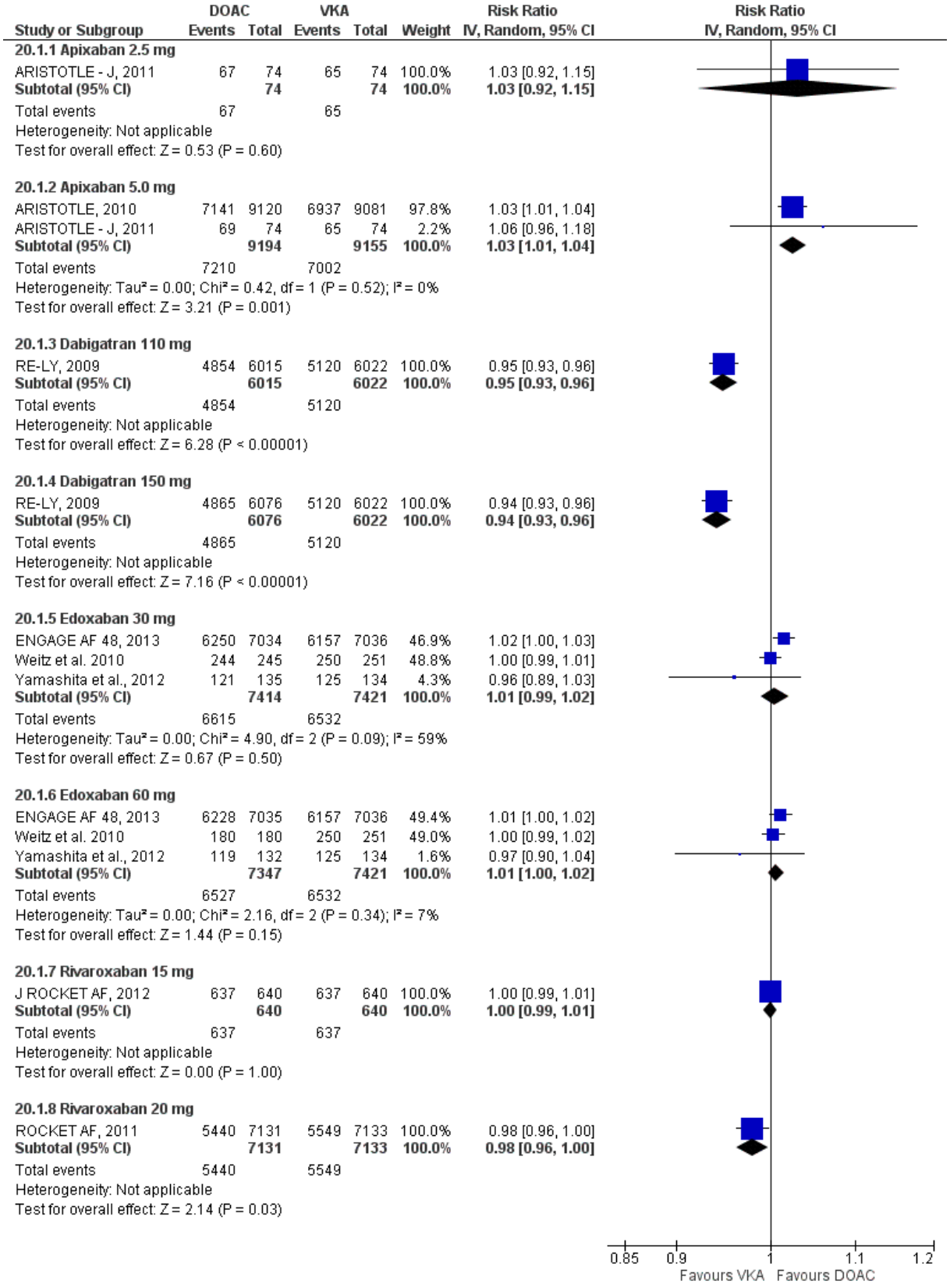
7.2.4.22 Adherence: NRSI evidence

None of the included NRSI reported medication adherence in NVAF patients.

7.2.4.23 Persistence: RCT evidence

RCT evidence for persistence, defined as the proportion of patients that continues therapy until completion of the follow-up period, was available for all DOACs (***Figure 30***). Persistence was statistically significantly in favour of apixaban 5 mg twice daily (low certainty evidence) compared to warfarin. In contrast, warfarin showed significantly better persistence compared to dabigatran 110 mg and 150 mg twice daily (moderate certainty evidence). For all other medications and doses, persistence was similar for DOACs compared to warfarin (low to high certainty evidence).

Figure 30 Persistence (RCTs)



Abbreviations:

CI: confidence interval**; DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist**.**

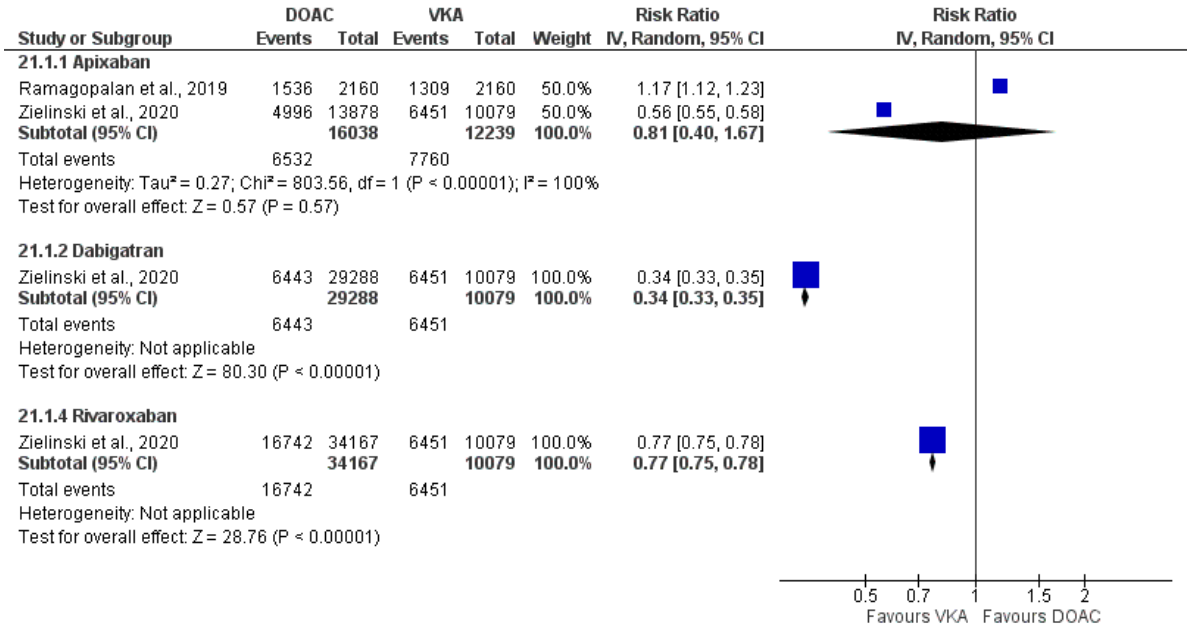
Notes:

Warfarin was the VKA used in all included trials.

7.2.4.24 Persistence: NRSI evidence

Apixaban was associated with no difference in treatment persistence compared to VKAs (very low certainty evidence) (***Figure 31***), whereas dabigatran and rivaroxaban showed significantly worse persistence compared to VKAs (low certainty evidence). It should be noted that the study by Zielinski et al 2020 reported unmatched, unadjusted RR analyses, thus it is subject to a very high risk of confounding.[94]

Figure 31 Persistence reported using RR (NRSIs)



Abbreviations

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

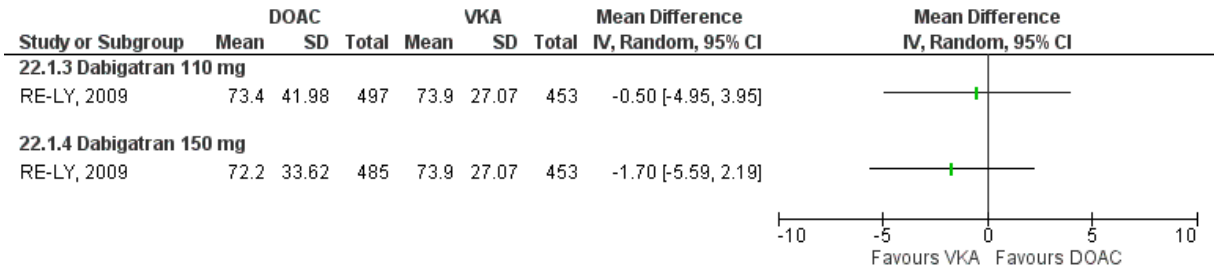
Notes

VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

7.2.4.25 Health-related quality of life: RCT evidence

HRQoL was reported by one RCT, which compared dabigatran (110 mg or 115 mg) to warfarin (***Figure 32***). No significant difference was reported for either formulation (low certainty evidence).

Figure 32 Health-related quality of life (RCTs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **SD:** standard deviation; **VKA:** vitamin-K antagonist.

Notes:

Warfarin was the VKA used in all included trials.

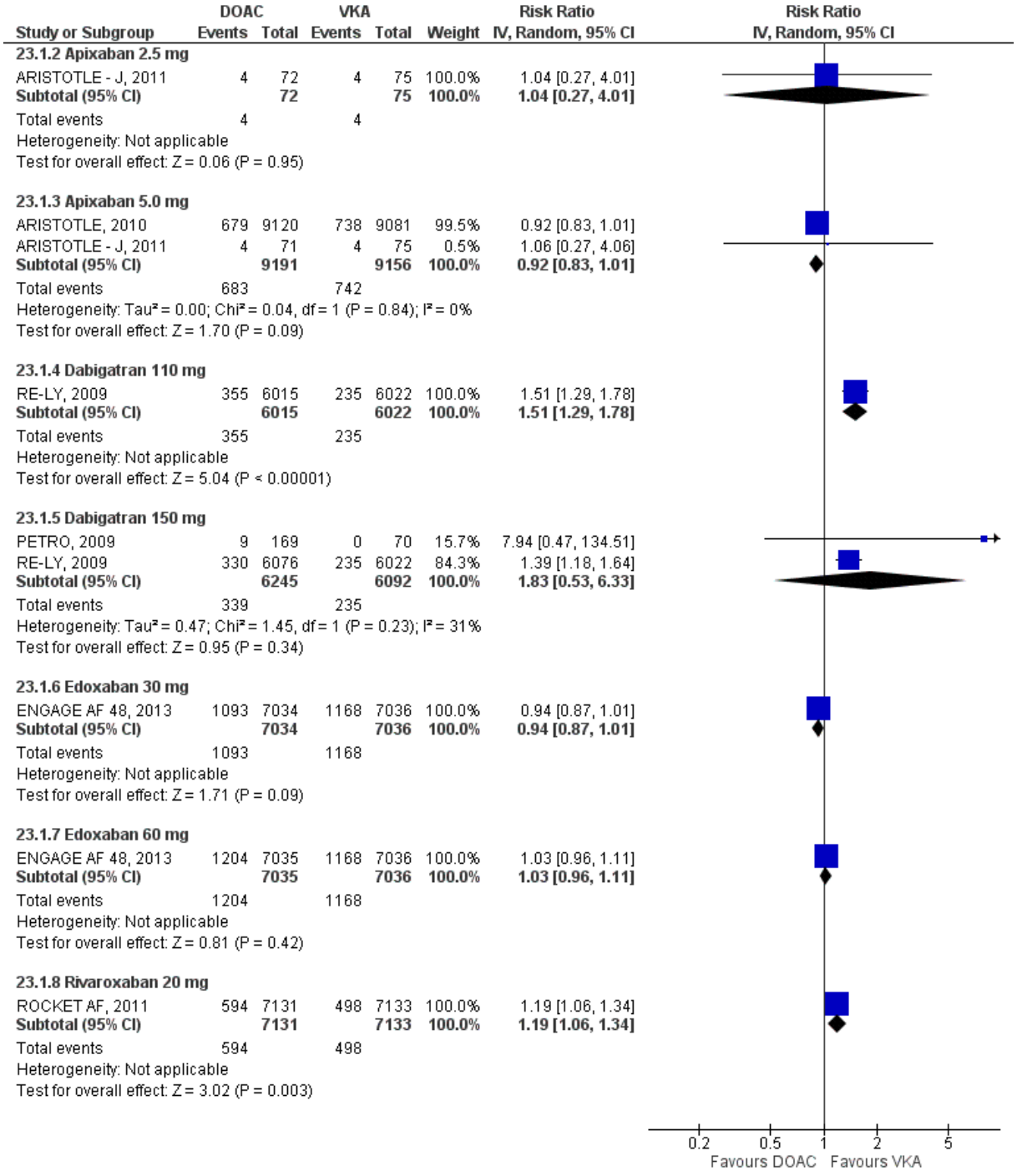
7.2.4.26 Health-related quality of life: NRSI evidence

None of the included NRSIs reported HRQoL-related outcomes in NVAF patients.

7.2.4.27 Treatment discontinuation due to adverse events: RCT evidence

Compared to warfarin, patients were statistically significantly more likely to discontinue due to adverse events as a result of dabigatran 110 mg twice daily (20 more per 1,000, from 11 more to 30 more; moderate certainty evidence) and rivaroxaban 20 mg once daily (13 more per 1,000, from 4 more to 24 more; high certainty evidence) (***Figure 33***). For all other DOACs there was no difference in discontinuation rates between DOACs and warfarin. Two comparisons were meta-analysed (apixaban 5 mg, dabigatran 150mg), which showed evidence of no or low heterogeneity.

Figure 33 Treatment discontinuation due to adverse events (RCTs)



Abbreviations:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **VKA:** vitamin-K antagonist.

Notes:

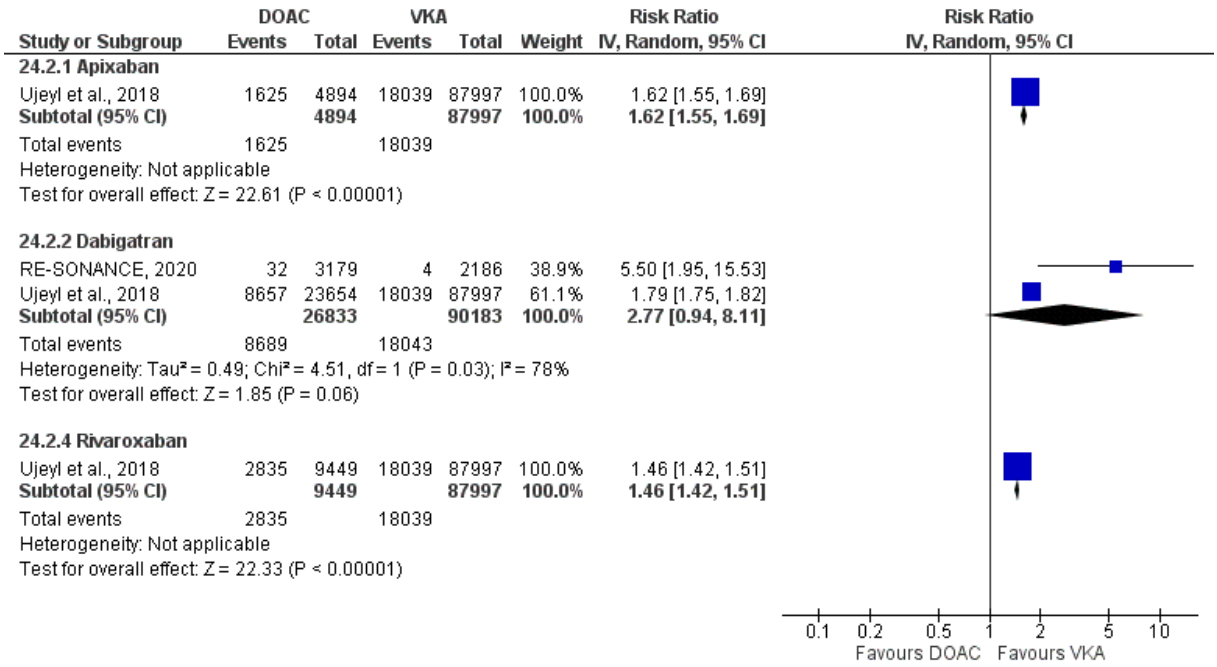
Warfarin was the VKA used in all included trials.

7.2.4.28 Treatment discontinuation due to adverse events: NRSI evidence

The RR analyses reported by the NRSIs found apixaban significantly increased the risk of treatment discontinuation due to adverse events (127 more per 1,000, from 113 more to 141 more; low certainty evidence), as did rivaroxaban (94 more per 1,000, from 86 more to 105 more; low certainty evidence) (***Figure 34***). Dabigatran was associated with a non-statistically significant increase in the risk of discontinuations (very low certainty evidence).

It should be noted that the RE-SONANCE trial reported unmatched, unadjusted RR analyses, thus is subject to a very high risk of confounding.[88]

Figure 34 Treatment discontinuation due to adverse events reported using RR (NRSIs)



Abbreviations:
CI: confidence interval; **DOAC**: direct-acting oral anticoagulants; **VKA**: vitamin-K antagonist.
Notes:
VKA used in all included trials was limited to acenocoumarol and phenprocoumon. Trials did not report intervention doses.

7.2.5 Applicability of the evidence

Applicability refers to the generalisability of the included studies to the Swiss context. It involves comparing demographics and clinical characteristics in the included studies to what generally occurs in Swiss practice.

7.2.5.1 Characterising the Swiss context for the treatment of NVAF

There is limited published literature reporting the demographic characteristics of Swiss NVAF patients; however, the demographic variables described by Stempfel (2020) were broadly consistent with the PICO criteria for this HTA report.[98] These authors examined symptoms and quality of life of 3,122

patients living with AF from 2 prospective, observational, multicentre cohort studies of AF patients in Switzerland: the BEAT-AF and Swiss-AF studies.[98]

Between 2010 and 2014, the BEAT-AF (Basel Atrial Fibrillation) cohort study recruited 1,553 patients with documented AF across 7 centres in Switzerland.[98] The Swiss-AF (Swiss Atrial Fibrillation) study enrolled 2,415 patients between 2014 and 2017 across 14 centres in Switzerland. In both cohorts, patients were required to have previously documented AF. They then completed a series of detailed questionnaires about personal, medical, nutritional and lifestyle factors to examine the potential burden of risk factors and comorbidities considered potential drivers for the increased risk of adverse outcome events.[98] Patients enrolled in BEAT-AF were ineligible for participation in Swiss-AF and vice versa.

Details around the use of DOACs and VKAs in Swiss practice have been informed by Swissmedic[41] and the Spezialitätenliste.[1]

An overview of the Swiss context for the treatment of NVAF is presented in ***Table 10***.

Table 10 Summary table characterising the Swiss context for the treatment of NVAF

Parameter	Characteristics
Demographics [98]	Average age (years): 72 ± 10 Sex, n female (% female): 924 (29.6%) Smoking status: current 245 (7.9%), history 1486 (47.6%), never 1388 (44.5%) Average body mass index (kg/m2): 27.4 ± 4.8 Average blood pressure (mm Hg): systolic 134 ± 19, diastolic 78 ± 12 History of hypertension: 2160 (69.2%) History of heart failure: 714 (22.9%) History of myocardial infarction: 462 (14.8%) History of stroke or transient ischaemic attack: 562 (18.0%) History of coronary artery disease: 802 (25.7%) History of renal failure: 557 (17.8%) Implanted device: 510 (16.3%) Average CHA2DS2-VASc score: 3.2 ± 1.8 Mean TTR ranged from 57.2% to 83% (median 62.2%)
Intervention(s) [1,41]	**Apixaban** [a]: listed on the Spezialitätenliste in a 5 mg formulation; listed on Swissmedic for the prevention of stroke and SE in adult patients with NVAF at 5 mg twice daily; the recommended dose is 2.5 mg twice daily in patients with at least 2 of the following criteria: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dl (133 µmol/l). **Dabigatran**: listed on the Spezialitätenliste in 110 mg or 150 mg formulations; listed on Swissmedic for the prevention of stroke and systemic embolism in adult patients with NVAF at 150 mg twice daily. The recommended dose for patients with moderate renal insufficiency (GFR 30–50 ml/min) is 110 mg. **Rivaroxaban** [b]: listed on the Spezialitätenliste in 10mg, 15 mg or 20 mg formulations; 10mg once daily is limited on the Spezialitätenliste for stroke prophylaxis and prophylaxis of systemic embolism in patients with NVAF and a simultaneous moderate renal impairment [creatinine clearance 30-49 ml/min], which must be additionally treated with a P2Y12 inhibitor due to percutaneous coronary intervention with stent insertion and in which a dose reduction to 10 mg once daily is therefore necessary; 15 mg once daily is recommended in patients with NVAF and moderate renal impairment; 20 mg once daily is recommended in patients with NVAF. **Edoxaban**: listed on the Spezialitätenliste in 15 mg, 30 mg and 60 mg formulations; listed on Swissmedic for the prophylaxis of stroke and systemic embolism in adult patients with NVAF at 60 mg

Parameter	Characteristics
	once daily. A dose of 30 mg is recommended for patients with moderate to serve renal insufficiency (GFR 15–50 ml/min), body weight ≤60 kg, have a valid prescription for P-glycoprotein inhibitors (e.g. cyclosporine)
Comparator(s) [1,41]	**Acenocoumarol**: listed on the Spezialitätenliste in 1 mg and 4 mg formulations; listed on Swissmedic for therapy and prophylaxis of thromboembolic diseases with a target INR 2.0–3.0, an average starting dose of 2.4–4 mg/day, and a usual maintenance dose of 1–8 mg/day. **Phenprocoumon**: listed on the Spezialitätenliste in a 3 mg formulation; listed on Swissmedic for thrombosis prophylaxis, thrombosis, embolism, heart attack, target INR 2.0–3.0 for patients with atrial fibrillation at a graduated initial dose of 4.5–9 mg in the first 3 days, and a usual maintenance dose of 1.5–4.5 mg/day. **Warfarin**: not currently used in Switzerland, see note in ***Section 5.3*** justifying the inclusion of warfarin as a comparator for the RCT analysis in this report. The average recommended dose for warfarin is 1.5–12mg/day.
Setting	Primary care setting or hospital General practitioner, cardiologist, haematologist

Abbreviations
AF: atrial fibrillation; **BMI**: body mass index; **CHA_2DS_2-VASc**: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female); **GFR**: glomerular filtration rate; **INR**: international normalised ratio; **NVAF**: non-valvular atrial fibrillation; **RCT**: randomised controlled trial; **SE**: systemic embolism; **TTR**: time in therapeutic range.
Notes
[a] A 2.5 mg formulation is listed on the Spezialitätenliste, listed on Swissmedic for the prevention of venous thromboembolic events (VTE) after elective hip or knee replacement surgery, and treatment of acute, deep vein thrombosis (DVT), treatment of pulmonary embolism (PE) and prevention of recurrent DVT and PE.
[b] A 2.5 mg formulation is listed on the Spezialitätenliste, limited for use in patients with chronic coronary heart disease or manifest peripheral arterial vascular disease and a high risk of ischemic events.

7.2.5.2 Applicability of the RCT evidence

There were no serious applicability concerns with the included RCT evidence. The populations broadly reflect the population of interest in Swiss practice in relation to age (average age ranged from 65 to 73 years), principal diagnosis (NVAF), gender (average proportion of females ranged from 19% to 44%), and comorbidity profiles. The median of mean TTRs reported in the RCTs were slightly lower than the observed median TTR observed in a Swiss cohort of 322 patients (65.5% vs 69%), noting that the range of reported mean TTR across the trials was within the interquartile range of the Swiss cohort (51% to 89%).[44] The ARISTOTLE trial included patients with AF or atrial flutter;[75] noting that it is unclear what proportion of patients had atrial flutter. The medications, dosages and regimens were in line with the approved listings on Swissmedic. The primary consideration for the applicability of the RCT to the Swiss context is the choice to include warfarin as the primary comparator. While not used in Switzerland, warfarin is conserved to be substantially equivalent alternative.

7.2.5.3 Applicability of the NRSI evidence

The populations included in the NRSIs were broadly reflective of the indicated population in Swiss practice. The populations broadly reflect the population of interest in Swiss practice in relation to age (average age ranged from 68–77 years), and principal diagnosis (NVAF), and comorbidity profiles; however, women were more represented compared to the Swiss-AF and BEAT-AF cohorts (average proportion of females ranged from 43% to 70%).[98]

The interventions (i.e. DOACs) and comparators (VKAs) studied in the NRSIs were the same as those used in Swiss practice, with a few minor concessions. Paschke et al 2020 included 2 drug dosages that are not approved for use in Switzerland: rivaroxaban 2.5 mg and dabigatran 75 mg;[89] however, the authors conducted sensitivity analyses removing these dosages from the main analysis, and found no impact on the results, suggesting that the results are reflective of the approved dosages. Two of the studies did not state what dosage of VKA was used.[91,92]

7.2.5.4 Discrepancies between the RCT and NRSI evidence

Conflicting results between the included RCTs and NRSIs for some outcomes are difficult to explain, but several reasons are explored here. One possible reason could be due to variation in the locations in which the studies took place—3 of the included studies (all RCTs) took place in Asian countries. There was also variability in the number and type of concomitant and prior medications used by patients between the RCTs and NRSIs. It is known that warfarin and other VKAs are affected by many factors including drug interaction, diet, and genetic variation in warfarin and vitamin K metabolism. The comparator for all the included RCTs was warfarin whereas for the NRSIs the VKA comparators were predominately phenprocoumon or acenocoumarol, with only 2 studies including a small percentage of patients treated with warfarin (0.5% and 14.0%, respectively). Finally, it should also be noted that dosage was poorly reported in the NRSIs, which made comparisons with the RCT data challenging. Similarly, length of follow-up varied between treatment groups within the NRSI studies.

7.2.6 GRADE evidence profile and summary of findings tables

The following tables (***Table 11*** to ***Table 17***) summarise the overall strength of evidence supporting the findings related to the safety and efficacy of the drugs under investigation. Per the GRADE approach, only key outcomes are reported in the summary-of-findings tables for each comparison.[60] These outcomes are reflected in the PICO criteria and in ***Section 7.1.4***.

Summary of findings tables have not been presented for the NRSI evidence for several reasons. First, there was an increased risk of bias due to unmeasured confounding and unbalanced, significant dropouts between arms in many studies. Further, some analyses reported heterogeneity in the reported results depending on which outcome measure was reported (i.e. HR or RR), which is not easily explained. Finally, many studies that reported HR did not report event rates, therefore absolute risks associated with the interventions cannot be calculated for the GRADE tables to provide context to the comparative result.

Tables reporting the GRADE evidence profiles for all outcomes and all levels of evidence are presented in ***Appendix C***. In all tables, the risk in the intervention group (and its 95% confidence interval) is based on the observed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

The certainty of evidence supporting an outcome, as scored according to the GRADE approach, is categorised as follows:[60]

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty**: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- **Very low certainty**: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Table 11 Summary of RCT findings for all-cause mortality compared to warfarin

Intervention	Anticipated absolute effects (95% CI)*		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with warfarin	Risk with Intervention			
All-cause mortality, *Figure 2*					
Apixaban 2.5 mg twice daily **Follow-up: 3 months**	not estimable	not estimable	not estimable	147 (1 RCT)	not estimable
Apixaban **5 mg twice daily** **Follow-up: 3 months to 21.6 months (median)**	66 per 1,000	**7 fewer per 1,000** (13 fewer to 0 fewer)	**RR 0.90** (0.81 to 1.00)	18,347 (2 RCTs)	⊕⊕◯◯ Low[a]
Dabigatran 110 mg twice daily **Follow-up: 24 months (mean)**	74 per 1,000	**6 fewer per 1,000** (14 fewer to 3 more)	**RR 0.92** (0.81 to 1.04)	12,037 (1 RCT)	⊕⊕⊕◯ Moderate[e]
Dabigatran 150 mg twice daily **Follow-up: 24 months (mean)**	81 per 1,000	**9 fewer per 1,000** (17 fewer to 1 more)	**RR 0.89** (0.79 to 1.01)	12,098 (1 RCT)	⊕⊕⊕◯ Moderate[e]
Edoxaban 30 mg once daily **Follow-up: 3 months to 29.8 months (median)**	114 per 1,000	**14 fewer per 1,000** (23 fewer to 5 fewer)	**RR 0.88** (0.80 to 0.96)	14,814 (3 RCTs)	⊕⊕⊕◯ Moderate[c]
Edoxaban 60 mg once daily **Follow-up: 3 months to 29.8 months (median)**	114 per 1,000	**9 fewer per 1,000** (18 fewer to 1 more)	**RR 0.92** (0.84 to 1.01)	14,814 (3 RCTs)	⊕⊕⊕◯ Moderate[a]
Rivaroxaban 15 mg once daily **Follow-up: 30 months**	8 per 1,000	**3 more per 1,000** (4 fewer to 27 more)	**RR 1.40** (0.45 to 4.39)	1,274 (1 RCT)	⊕⊕◯◯ Low[b,d]
Rivaroxaban 20 mg once daily **Follow-up: 19.4 months (median)**	89 per 1,000	**7 fewer per 1,000** (15 fewer to 3 more)	**RR 0.92** (0.83 to 1.03)	14,171 (1 RCT)	⊕⊕⊕⊕ High

Abbreviations:
CI: confidence interval; **NR:** not reported; **RCT**: randomised controlled trial; **RR**: risk ratio.
Notes:
[a] Downgraded due to a high risk of selection, blinding, incomplete outcome data.
[b] Downgraded due to imprecision owing to wide confidence intervals and low event rates.
[c] Downgraded due to a high risk of incomplete outcome data.
[d] Downgraded due to a high risk of selection bias.
[e] Downgraded due to inadequate blinding.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 12 Summary of RCT findings for major/life-threatening bleeding compared to warfarin

Intervention	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with warfarin	Risk with Intervention			
Major/life-threatening bleeding, *Figure 8*					
Apixaban 2.5 mg twice daily **Follow-up: 21.6 months (median)**	13 per 1,000	**9 fewer per 1,000** (13 fewer to 98 more)	RR 0.35 (0.01 to 8.38)	147 (1 RCT)	⊕◯◯◯ Very low[a,b]
Apixaban **5 mg twice daily** **Follow-up: 3 months to 21.6 months (median)**	51 per 1,000	**15 fewer per 1,000** (20 fewer to 10 fewer)	**RR 0.70** (0.61 to 0.81)	18,286 (2 RCTs)	⊕⊕◯◯ Low[a]
Dabigatran 110 mg twice daily **Follow-up: 24 months (mean)**	70 per 1,000	**13 fewer per 1,000** (20 fewer to 5 fewer)	**RR 0.81** (0.71 to 0.93)	12,037 (1 RCT)	⊕⊕⊕◯ Moderate[c]
Dabigatran 150 mg twice daily **Follow-up: 3 months to 24 months (mean)**	69 per 1,000	**4 fewer per 1,000** (12 fewer to 5 more)	**RR 0.94** (0.82 to 1.07)	12,268 (2 RCTs)	⊕⊕⊕◯ Moderate[a]
Edoxaban 30 mg once daily **Follow-up: 3 months to 29.8 months (median)**	71 per 1,000	**36 fewer per 1,000** (41 fewer to 31 fewer)	**RR 0.49** (0.42 to 0.56)	14,754 (3 RCTs)	⊕⊕⊕◯ Moderate[a]
Edoxaban 60 mg once daily **Follow-up: 3 months to 29.8 months (median)**	71 per 1,000	**14 fewer per 1,000** (21 fewer to 6 fewer)	**RR 0.80** (0.71 to 0.91)	14,754 (3 RCTs)	⊕⊕⊕◯ Moderate[a]
Rivaroxaban 15 mg once daily	NR	-	-	-	-
Rivaroxaban 20 mg once daily **Follow-up: 19.4 months (median)**	54 per 1,000	**2 more per 1,000** (6 fewer to 10 more)	**RR 1.03** (0.89 to 1.18)	14,236 (1 RCT)	⊕⊕⊕⊕ High

Abbreviations:

CI: confidence interval; **RCT**: randomised controlled trial; **RR**: risk ratio.

Notes:

[a] Downgraded due to a high risk of selection, blinding, incomplete outcome data.

[b] Downgraded due to imprecision owing to wide confidence intervals and low event rates.

[c] Downgraded due to inadequate blinding.

* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 13 Summary of RCT findings for stroke and systemic embolic events compared to warfarin

Intervention	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with warfarin	Risk with Intervention			
Stroke and systemic embolic events, *Figure 20*					
Apixaban 2.5 mg twice daily **Follow-up: 3 months**	53 per 1,000	**47 fewer per 1,000** (53 fewer to 59 more)	**RR 0.12** (0.01 to 2.11)	147 (1 RCT)	⊕◯◯◯ Very low[a,d]
Apixaban **5 mg twice daily** **Follow-up: 3 months to 21.6 months (median)**	29 per 1,000	**14 fewer per 1,000** (26 fewer to 43 more)	**RR 0.54** (0.12 to 2.45)	18,347 (2 RCTs)	⊕◯◯◯ Very low[a,b]
Dabigatran 110 mg twice daily **Follow-up: 24 months (mean)**	34 per 1,000	**3 fewer per 1,000** (9 fewer to 3 more)	**RR 0.91** (0.74 to 1.10)	12,037 (1 RCT)	⊕⊕⊕◯ Moderate[h]
Dabigatran 150 mg twice daily **Follow-up: 3 months to 24 months (mean)**	33 per 1,000	**3 fewer per 1,000** (9 fewer to 3 more)	**RR 0.91** (0.74 to 1.10)	12,217 (2 RCTs)	⊕⊕⊕◯ Moderate[a]
Edoxaban 30 mg once daily **Follow-up: 3 months to 29.8 months (median)**	46 per 1,000	**7 fewer per 1,000** (34 fewer to 77 more)	**RR 0.84** (0.27 to 2.67)	14,814 (3 RCTs)	⊕◯◯◯ Very low[a,e,f]
Edoxaban 60 mg once daily **Follow-up: 3 months to 29.8 months (median)**	46 per 1,000	**9 fewer per 1,000** (25 fewer to 20 more)	**RR 0.81** (0.46 to 1.44)	14,814 (3 RCTs)	⊕⊕◯◯ Low[a,f]
Rivaroxaban 15 mg once daily **Follow-up: 30 months**	35 per 1,000	**17 fewer per 1,000** (26 fewer to 1 more)	**RR 0.50** (0.24 to 1.02)	1,274 (1 RCT)	⊕⊕◯◯ Low[b,c]
Rivaroxaban 20 mg once daily **Follow-up: 19.4 months (median)**	43 per 1,000	**5 fewer per 1,000** (11 fewer to 1 more)	**RR 0.88** (0.75 to 1.03)	14,171 (1 RCT)	⊕⊕⊕⊕ High

Abbreviations:

CI: confidence interval; **RCT**: randomised controlled trial; **RR**: risk ratio.

Notes:

[a] Downgraded due to a high risk of selection, blinding, incomplete outcome data.

[b] Downgraded due to imprecision owing to wide confidence intervals and low event rates.

[c] Downgraded due to a high risk of selection bias.

[d] Downgraded due to imprecision owing to very wide confidence intervals and low event rates.

[e] Downgraded due to inconsistency owing to the presence moderate heterogeneity.

[f] Downgraded due to imprecision owing to small study effects impacting the variance in the effect estimate.

[h] Downgraded due to inadequate blinding

** The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 14 Summary of RCT findings for ischaemic stroke compared to warfarin

Intervention	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with warfarin	Risk with Intervention			
Ischaemic stroke, *Figure 23*					
Apixaban 2.5 mg twice daily	NR	-	-	-	-
Apixaban 5 mg twice daily Follow-up: 21.6 months (median)	19 per 1,000	**2 fewer per 1,000** (5 fewer to 3 more)	**RR 0.92** (0.75 to 1.14)	18,201 (1 RCT)	⊕⊕◯◯ Low[a]
Dabigatran 110 mg twice daily Follow-up: 24 months (mean)	24 per 1,000	**3 more per 1,000** (2 fewer to 9 more)	**RR 1.12** (0.90 to 1.40)	12,037 (1 RCT)	⊕⊕⊕◯ Moderate[d]
Dabigatran 150 mg twice daily Follow-up: 24 months (mean)	24 per 1,000	**5 fewer per 1,000** (9 fewer to 0 fewer)	**RR 0.77** (0.61 to 0.99)	12,098 (1 RCT)	⊕⊕⊕◯ Moderate[d]
Edoxaban 30 mg once daily Follow-up: 29.8 months (median)	33 per 1,000	**14 more per 1,000** (7 more to 25 more)	**RR 1.42** (1.20 to 1.76)	14,070 (1 RCT)	⊕⊕⊕⊕ High
Edoxaban 60 mg once daily Follow-up: 29.8 months (median)	33 per 1,000	**0 fewer per 1,000** (5 fewer to 7 more)	**RR 1.00** (0.84 to 1.20)	14,071 (1 RCT)	⊕⊕⊕⊕ High
Rivaroxaban 15 mg once daily Follow-up: 30 months	27 per 1,000	**16 fewer per 1,000** (22 fewer to 0 fewer)	**RR 0.41** (0.17 to 0.99)	1,278 (1 RCT)	⊕⊕◯◯ Low[b,c]
Rivaroxaban 20 mg once daily Follow-up: 19.4 months (median)	21 per 1,000	**1 fewer per 1,000** (5 fewer to 3 more)	**RR 0.93** (0.74 to 1.16)	14,875 (1 RCT)	⊕⊕⊕⊕ High

Abbreviations:

CI: confidence interval; **RCT**: randomised controlled trial; **RR**: risk ratio.

Notes:

[a] Downgraded due to a high risk of selection, blinding, incomplete outcome data.

[b] Downgraded due to imprecision owing to wide confidence intervals and low event rates.

[c] Downgraded due to a high risk of selection bias.

[d] Downgraded due to inadequate blinding.

* Control group risk is a weighted average of the absolute risk observed in the trials. Relative effects are based on the meta-analysis results.

Table 15 Summary of RCT findings for intracranial bleeding compared to warfarin

Intervention	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with warfarin	Risk with Intervention			
Intracranial bleeding, *Figure 11*					
Apixaban 2.5 mg twice daily	NR	-	-	-	-
Apixaban 5 mg twice daily Follow-up: 21.6 months (median)	13 per 1,000	**8 fewer per 1,000** (9 fewer to 6 fewer)	**RR 0.42** (0.31 to 0.59)	18,140 (1 RCT)	⊕⊕◯◯ Low[a]
Dabigatran 110 mg twice daily Follow-up: 24 months (mean)	14 per 1,000	**10 fewer per 1,000** (12 fewer to 8 fewer)	**RR 0.31** (0.20 to 0.48)	12,037 (1 RCT)	⊕⊕⊕◯ Moderate[d]
Dabigatran 150 mg twice daily Follow-up: 24 months (mean)	14 per 1,000	**9 fewer per 1,000** (10 fewer to 6 fewer)	**RR 0.41** (0.28 to 0.60)	12,098 (1 RCT)	⊕⊕⊕◯ Moderate[d]
Edoxaban 30 mg once daily Follow-up: 29.8 months (median)	19 per 1,000	**13 fewer per 1,000** (15 fewer to 11 fewer)	**RR 0.31** (0.22 to 0.44)	14,014 (1 RCT)	⊕⊕⊕⊕ High
Edoxaban 60 mg once daily Follow-up: 29.8 months (median)	19 per 1,000	**10 fewer per 1,000** (12 fewer to 7 fewer)	**RR 0.46** (0.34 to 0.62)	14,132 (1 RCT)	⊕⊕⊕⊕ High
Rivaroxaban 15 mg once daily Follow-up: 30 months	16 per 1,000	**8 fewer per 1,000** (13 fewer to 7 more)	**RR 0.50** (0.17 to 1.45)	1,278 (1 RCT)	⊕⊕◯◯ Low[b,c]
Rivaroxaban 20 mg once daily Follow-up: 30 months	12 per 1,000	**4 fewer per 1,000** (6 fewer to 1 fewer)	**RR 0.66** (0.47 to 0.92)	14,236 (1 RCT)	⊕⊕⊕⊕ High

Abbreviations:
CI: confidence interval; **RCT**: randomised controlled trial; **RR**: risk ratio.
Notes:
[a] Downgraded due to a high risk of selection, blinding, incomplete outcome data.
[b] Downgraded due to imprecision owing to wide confidence intervals and low event rates.
[c] Downgraded due to a high risk of selection bias.
[d] Downgraded due to inadequate blinding.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 16 Summary of findings table treatment adherence compared to warfarin

Intervention	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with warfarin	Risk with Intervention			
Treatment adherence, *Figure 29*					
Apixaban 2.5 mg twice daily	NR	-	-	-	-
Apixaban 5 mg twice daily	NR	-	-	-	-
Dabigatran 110 mg twice daily	NR	-	-	-	-
Dabigatran 150 mg twice daily	NR	-	-	-	-
Edoxaban 30 mg once daily	NR	-	-	-	-
Edoxaban 60 mg once daily	NR	-	-	-	-
Rivaroxaban 15 mg once daily	NR	-	-	-	-
Rivaroxaban 20 mg once daily **Follow-up: 19.4 months (median)**	977 per 1,000	**0 fewer per 1,000** (0 fewer to 10 more)	**RR 1.00** (1.00 to 1.01)	14,236 (1 RCT)	⨁⨁⨁⨁ High

Abbreviations:
CI: confidence interval; **RCT**: randomised controlled trial; **RR**: risk ratio.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 17 Summary of RCT findings for discontinuation due to adverse events compared to warfarin

Intervention	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with warfarin	Risk with Intervention			
Discontinuation due to adverse events, *Figure 33*					
Apixaban 2.5 mg twice daily **Follow-up: 3 months**	53 per 1,000	**2 more per 1,000** (39 fewer to 161 more)	**RR 1.04** (0.27 to 4.01)	147 (1 RCT)	⊕◯◯◯ Very low[a,b]
Apixaban **5 mg twice daily** **Follow-up: 3 months to 21.6 months (median)**	81 per 1,000	**6 fewer per 1,000** (14 fewer to 1 more)	**RR 0.92** (0.83 to 1.01)	18,347 (2 RCTs)	⊕⊕◯◯ Low[a]
Dabigatran 110 mg twice daily **Follow-up: 24 months (mean)**	39 per 1,000	**20 more per 1,000** (11 more to 30 more)	**RR 1.51** (1.29 to 1.78)	12,037 (1 RCT)	⊕⊕⊕◯ Moderate[c]
Dabigatran 150 mg twice daily **Follow-up: 3 months to 24 months (mean)**	39 per 1,000	**15 more per 1,000** (7 more to 25 more)	**RR 1.39** (1.18 to 1.64)	12,098 (1 RCT)	⊕⊕⊕◯ Moderate[c]
Edoxaban 30 mg once daily **Follow-up: 29.8 months (median)**	166 per 1,000	**10 fewer per 1,000** (22 fewer to 2 more)	**RR 0.94** (0.87 to 1.01)	14,070 (1 RCT)	⊕⊕⊕⊕ High
Edoxaban 60 mg once daily **Follow-up: 29.8 months (median)**	166 per 1,000	**5 more per 1,000** (7 fewer to 18 more)	**RR 1.03** (0.96 to 1.11)	14,071 (1 RCT)	⊕⊕⊕⊕ High
Rivaroxaban 15 mg once daily	NR	**-**	**-**	-	-
Rivaroxaban 20 mg once daily **Follow-up: 19.4 months (median)**	70 per 1,000	**13 more per 1,000** (4 more to 24 more)	**RR 1.19** (1.06 to 1.34)	14,264 (1 RCT)	⊕⊕⊕⊕ High

Abbreviations:
CI: confidence interval; **OR**: odds ratio; **RCT**: randomised controlled trial; **RR**: risk ratio.
Notes:
[a] Downgraded due to a high risk of selection, blinding, incomplete outcome data.
[b] Downgraded due to imprecision owing to wide confidence intervals and low event rates.
[c] Downgraded due to inadequate blinding.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

8 Costs, cost-effectiveness and budget impact

Summary statement costs, cost-effectiveness and budget impact

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A Markov model was developed to evaluate—from the perspective of the Swiss healthcare payer—the cost-effectiveness of apixaban, dabigatran, edoxaban and rivaroxaban relative to VKAs for the prevention of stroke and SE in patients with AF. Four pairwise analyses were undertaken to evaluate the cost-effectiveness of each DOAC individually, relative to the VKA drug class.

Under base-case assumptions, all DOACs were found to be cost-saving compared to VKAs while improving patient outcomes (i.e. quality-adjusted life years [QALYs] lived). All DOACs increased drug costs relative to VKAs but were cost-saving in terms of monitoring and clinical event costs. Sensitivity analyses found the dominance of each DOAC to be robust. The relative efficacy of each DOAC with respect to all-cause mortality was the main model driver in all 4 comparisons. The assumed interval between INR testing for patients on a VKA and the baseline hazard of intracranial haemorrhage (ICH) were also drivers. The high monitoring costs associated with VKAs proved influential; removing this reverted the dominance of all 4 DOACs.

The higher effectiveness of DOACs relative to VKAs observed in RCTs was not consistently reflected in the NRSI data (***Section 7.2.4***). These inconsistent findings significantly impacted the economic outcomes; analyses based on the NRSI HRs generally (except for dabigatran) supporting the cost effectiveness of VKAs rather than DOACs. Nevertheless, conclusions regarding the cost-effectiveness of DOACs were drawn based on the RCT-based analyses alone because the NRSI evidence itself was conflicting and difficult to interpret. Overall, the economic evaluation supported the cost-effectiveness of DOACs.

Under current policy conditions, OACs for patients with AF were estimated to be responsible for a cost of CHF128.0 million in 2021, increasing to an anticipated cost of CHF188.2 million in 2026. Expected monitoring costs were projected to decline from an estimated CHF88.4 million in 2021 to CHF44.7 million in 2026. Overall, treatment costs (i.e. drug and monitoring costs combined) were projected to rise to an anticipated CHF233.0 million in 2026.

8.1 Methodology: costs, cost-effectiveness and budget impact

8.1.1 Study selection

The systematic literature searches outlined in ***Section 7.1.1*** were used to identify studies assessing the cost-effectiveness of DOACs for the prevention of stroke in patients with NVAF. In addition, the reference lists of recent systematic reviews were hand-searched for cost-effectiveness studies not captured in the database searches.

Full economic evaluations (studies that value both costs and benefits of different treatments) that met the PICO and study selection criteria and were published after 2012 were included. As per the study selection criteria (see ***Section 7.1.2***), inclusion was limited to studies performed from the perspective of a World Health Organization (WHO) Mortality Stratum A country.

Only Swiss-specific economic evaluations including all relevant interventions were considered directly applicable to the HTA key question.

8.1.2 Data extraction, analysis and synthesis

Due to the absence of directly applicable evidence, identified cost-effectiveness studies were reviewed with the purpose of informing the methodology for an independent evaluation. Data extraction focused on key model design features (i.e. country, perspective, model type, time horizon, cycle length, interventions considered, clinical events, health states, structural assumptions and reference model). Data extraction was completed by one reviewer and checked by a second reviewer. The completed extraction template is available upon request.

Study characteristics and modelling features of the existing evidence were described narratively.

8.1.3 Economic modelling

Due to the absence of directly applicable evidence, de novo economic modelling was performed. A state-transition (Markov) model was developed to estimate the expected costs and QALYs associated with DOACs compared to VKAs for an average patient with NVAF over a lifetime horizon. The model captures the main clinical outcomes of anticoagulated patients with NVAF, including stroke and bleed events. The model was developed in TreeAge Pro (Version 2022 R2.0).[99]

Despite not being directly applicable to the HTA context, many existing models were aligned in the main domains, such as the population modelled, interventions considered and outcome measure used. The existing evidence base informed the economic modelling undertaken.

8.1.3.1 Evaluation perspective

A Swiss healthcare payer perspective was adopted. Direct medical costs for services covered by mandatory health insurance (OKP) were considered. Non-medical and indirect costs (e.g. travel costs, informal care or productivity losses) were not included. Healthcare resources associated with DOACs and VKAs were identified, measured and valued in 2022 Swiss Francs (CHF).

Effectiveness was measured in terms of QALYs lived, a final health outcome. Both costs and effects were discounted at 3.0% per annum.

8.1.3.2 Method used to generate results

Cohort expected value analysis via Markov modelling was used to generate the results. Each DOAC was individually compared against the VKA drug class in 4 pairwise comparisons. Results were expressed as incremental cost per QALY gained.

Uncertainties in the base case estimates were explored using one-way deterministic sensitivity analysis (DSA), scenario analysis and probabilistic sensitivity analysis (PSA). One-way DSA was used to identify the key model drivers of each pairwise comparison. Scenario analysis was used to explore the impact of certain structural assumptions. PSA was used to capture the joint uncertainty across model parameters, giving decision-makers information on the overall certainty of the economic outcomes.

One-way DSA outcomes were presented using tornado diagrams while PSA outcomes were presented as 95% confidence ellipses on the cost-effectiveness (CE) plane and as cost-effectiveness acceptability curves (CEACs).

There is no accepted willingness to pay (WTP) threshold in Switzerland. Using CEACs curves produced via PSAs, the probability of cost-effectiveness was expressed as a function of WTP.

8.1.3.3 Budget impact analysis

Budget impact analysis (BIA) was undertaken to explore the expected costs of OAC therapies to the OKP over the period 2022 to 2026.

The number of treated NVAF patients in Switzerland was estimated using an epidemiological approach. Despite DOACs already being reimbursed, a market share approach was not utilised given challenges in identifying NVAF-specific utilisation (sales data are not specific for the indication of NVAF) and in incorporating annual coverage rates (i.e. treated days per year). The number of treated NVAF patients was estimated for the year 2021 and extrapolated over the period 2022 to 2026, accounting for expected demographic changes in the Swiss population.

The base scenario estimated the expected payer costs under current policy conditions, with the proportion of anticoagulated AF patients receiving DOAC vs VKA being extrapolated based on recent

trends. The financial implications of potential policy changes (i.e. restriction of or disinvestment from DOAC) were not modelled, given findings of the clinical and economic evidence did not justify any such scenarios.

8.2 Results: costs, cost-effectiveness and budget impact

8.2.1 Search results

A PRISMA flowchart summarising the overall systematic literature searches is available in ***Section 7.2.2***. In total, 55 full economic evaluations were identified.

8.2.2 Systematic review: summary of findings

8.2.2.1 Study characteristics

The retrieved studies included economic evaluations from a number of WHO Mortality Stratum A countries, including Austria,[100] Australia,[101] Belgium,[102-104] Canada,[105] Finland,[106,107] France,[108-111] Germany,[112-114] Greece,[115-117] Italy,[118-122] Japan,[123,124] the Netherlands,[125-129] Norway,[130] Portugal,[131,132] Singapore,[133,134] Slovenia,[135] Spain,[136,137] Sweden,[138,139] Switzerland,[140] the United Kingdom,[44,128,141-143] and the United States.[144-152]

Most studies adopted a healthcare payer perspective. A few studies published within the Dutch,[125,126,129] Portuguese,[132] Spanish,[137] Swedish,[138,139] and United States contexts[147,148,150,151] adopted a broader, societal perspective.

Thirty studies compared a single DOAC to VKAs; 9 considering apixaban,[101,106,117,124,127,137,139,142,145] 10 dabigatran,[102,108,109,116,122,126,138,140,147,152] 4 edoxaban,[120,136,149,151] and 7 rivaroxaban.[103,110,112,115,123,129,132] Two studies included 2 DOACs; one considered both apixaban and rivaroxaban,[141] the other, dabigatran and rivaroxaban.[134] Fourteen studies included 3 DOACs, all of which considered apixaban, dabigatran and rivaroxaban but not edoxaban.[104,105,107,111,113,119,121,128,130,131,143,148,150,153] Nine studies considered all 4 DOACs of interest (apixaban, dabigatran, edoxaban, rivaroxaban).[44,100,114,125,133,135,144,146,154]

In some healthcare settings, VKAs other than warfarin were prescribed. While most studies specified warfarin as the comparator, some considered acenocoumarol and/or phenprocoumon (within Belgian, Dutch, German, Greek, Spanish or Swiss contexts),[102,114-116,125-127,129,136,137,140] or other VKAs (i.e. fluindione within a French context).[108,109] The use of other VKAs affected cost inputs only, as therapeutic equivalence was assumed across the VKA class (i.e. between warfarin and other VKAs).

All but one of the included studies employed a Markov (state-transition) model. The time horizon of the Markov models varied between 10 years and lifetime, while the cycle lengths varied between 30 days (1 month) and 1 year. Most of the Markov models were analysed as cohort models, with only a few

employing microsimulations. The study that did not use a Markov model employed a decision tree to estimate the cost-effectiveness of rivaroxaban vs VKAs over a one-year time horizon using real-world data.[129]

Reference models were identified, which have been adapted for use in several published cost-effectiveness evaluations. A summary of these reference models is provided in ***Table 18***. A list of studies referencing each of these reference models is available in ***Appendix D*** (***Table 124***).

Table 18 Summary of the 4 reference models

Reference model	Notes
Bayer [103,155,156]	Submitted to NICE to inform its evaluation of rivaroxaban for the prevention of stroke and SE in people with AF (Technology Appraisal 256).[156] Almost all adaptations have considered a pairwise comparison between rivaroxaban and VKA.
Dorian [142,157]	Developed to assess the cost-effectiveness of apixaban in the following comparisons: • vs warfarin in people with NVAF suitable for VKAs[142] • vs aspirin in people with NVAF unsuitable for VKAs[142] • vs dabigatran and rivaroxaban in people with NVAF suitable for VKAs[157] Most adaptations consider apixaban as the reference, comparing apixaban to VKA ± aspirin or other DOACs.
López-López [44,158,159]	Published alongside a systematic review and network meta-analysis, and developed to assess the most cost-effective first-line anticoagulant for the prevention of stroke in patients with AF, from the perspective of the UK healthcare payer. The model has since been adapted to inform different research questions: cost-effectiveness of apixaban vs other DOACs and VKAs; cost-effectiveness of DOACs vs VKAs.
Sorensen [143,160-162]	The conceptual framework was first developed to assess the cost-effectiveness of different warfarin treatment scenarios.[160] It has since been used to assess the cost-effectiveness of dabigatran vs warfarin in Canada[161] and the UK.[162] The model was later updated to consider the effect of MI history on the risk of future MI and long-term QoL and costs. This was done as part of an evaluation that assessed the cost-effectiveness of dabigatran vs warfarin, apixaban and rivaroxaban in the UK setting.[143] All adaptations have considered dabigatran as the reference drug, the majority considering a pairwise comparison between dabigatran and VKAs.

Abbreviations:
AF: atrial fibrillation; **MI**: myocardial infarction; **NICE**: National Institute for Health and Care Excellence; **NVAF**: non-valvular atrial fibrillation; **SE**: systemic embolism; **QoL**: quality of life; **VKA**: vitamin K antagonist

8.2.2.2 Modelling features

The most commonly modelled clinical outcomes included ischemic stroke (IS), haemorrhagic stroke (HS), transient ischemic attack (TIA), SE, myocardial infarction (MI), intracranial haemorrhage (ICH), major extracranial bleeds and minor bleeding. Most models considered some events to be transient in nature and others—notably, stroke (ischemic and haemorrhagic) and other intracranial bleeds—to be associated with long-term consequences.

The severity of stroke events was incorporated in varying ways across models. Some models included distinct health states for the various severity levels. For example, the *Dorian model* included distinct states for minor, moderate and severe strokes (ischemic or haemorrhagic),[142] while the *Sorensen model*

modelled the consequential disabilities of IS or ICH, including distinct states to capture varying disability levels (independent, moderately dependent or totally dependent). While the health states used in the *Dorian model* directly captured patient history of IS or HS, the *Sorensen model* tracked patient history of stroke (defined as prior IS or TIA) independently of disability level.[161] The *López-López model* did not distinguish between stroke severities within its structure, instead valuing the cost and quality of life (QoL) impacts of stroke as an average across severities.[44,158]

The included studies made varying assumptions regarding drug persistence. Many made specific assumptions about what would happen after a clinical event—for example, assuming permanent or temporary discontinuations after haemorrhage. Some also, or alternatively, modelled treatment discontinuations unrelated to the modelled events. Studies made varying assumptions as to whether patients would switch to a second-line treatment such as aspirin, or receive no further antithrombotic treatment upon discontinuation of the initially assigned OAC.

While earlier cost-effectiveness studies were largely based on the pivotal RCTs for each DOAC, more recent studies have used data from network meta-analyses (NMA) of RCT evidence,[44,100] or from real-world evidence.[107,110,141,153] Some have focused on comparing results between RCT and real-world data.[109,125,144] Others have used baseline event rates from country- or region-specific real-world data and treatment effect estimates from RCTs.[130,146,154]

Some studies were interested in comparing cost-effectiveness results between patient sub-populations—for example, patients with varying levels of kidney function,[145] start age,[133] stroke and/or bleed risk,[119,130,147,154] quality of INR control on VKAs,[128,129] and VKA-suitable vs unsuitable patients.[142]

8.2.3 Decision regarding use or adaptation of existing results

Only Swiss-specific economic evaluations including all relevant interventions were considered directly applicable to the HTA context. A previous study evaluated the cost-effectiveness of dabigatran vs VKA for stroke prevention in Swiss patients with AF;[140] however, the study was only partially applicable to the policy question of this HTA, as it did not evaluate the cost-effectiveness of apixaban, rivaroxaban or edoxaban.

A large volume of published evidence on the cost-effectiveness of DOACs in NVAF populations across several WHO Mortality Stratum A countries exists; however, there are limitations in translating the results of existing evaluations to the Swiss context. Due to the absence of directly applicable studies, an evaluation of the cost-effectiveness of DOACs compared to VKAs among Swiss patients with NVAF was performed.

Nevertheless, many existing models were aligned in several domains, such as the population modelled, interventions considered and outcome measure used. The *López-López model* included all interventions

of interest, considered a similar population to that of interest for this HTA (i.e. patients with NVAF who are eligible for anticoagulation), and sourced event rates and relative treatment effects from an NMA of RCT evidence that was identified in scoping as being up-to-date and of high quality. Thus, this model has, where appropriate, informed the model design and inputs for this HTA. Where necessary, changes were made to adapt the evaluation to the HTA context.

8.2.4 Economic model: structure

As with most existing models, a state-transition (Markov) cohort model was constructed. The model consisted of 5 health states and 6 clinical events or transitions states, as detailed below. These reflected a selection, but not all, of the health states and events included in the *López-López model.*

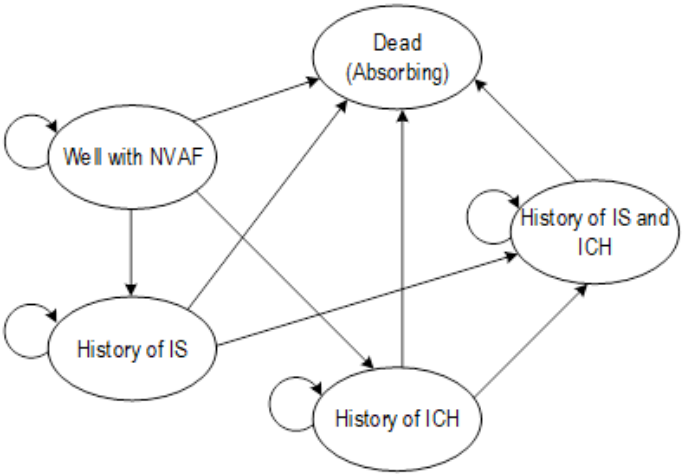
In brief, the model considered the following clinical outcomes: IS, ICH, major extracranial bleeds, SE and mortality (all-cause). Neither MI nor TIA were considered, given they are not included in the standard outcome sets for AF to which the PICO guiding this HTA was aligned. Outcomes included in the PICO were developed in accordance with the key outcomes recommended by the European Medicines Agency and the International Consortium for Health Outcomes Measurement (ICHOM).[45,46] Health states in a previous model developed to evaluate the cost-effectiveness of rivaroxaban within the German context (the *Mensch model*) include neither MI nor TIA, in accordance with relevant outcomes stated in European Guidelines.[46,112] In a further similarity to the *Mensch model*, major extracranial bleeds as a transient event were included in this HTA.

In line with the *López-López model,* the model structure did not distinguish between minor IS and major IS.[44] Similar to the *López-López model* and other previous models, the model for this HTA used memory states to record patient history of the most important clinical events (IS, ICH [including haemorrhagic stroke] and death). Additional clinical outcomes (major extracranial bleeds and SE) were considered as transient events, having short-term effects on costs and QoL but not affecting the health state in which a patient resides (i.e. not affecting ongoing health status).

8.2.4.1 Health states

The 5 health states were: well with NVAF (i.e. with no history of IS or ICH), IS (i.e. with history of prior IS), ICH (i.e. with history of prior ICH), IS and ICH (i.e. with history of prior IS and ICH), and dead (***Figure 35***). These states act as memory states to track a patient's history of IS and ICH.

Figure 35 Markov model: state transition diagram



Abbreviations:
ICH: intracranial haemorrhage; **IS**: ischaemic stroke; **NVAF**: nonvalvular atrial fibrillation.

Histories of IS and ICH events were tracked, given they can impact future risk of clinical events, patient HRQoL and future treatment decisions.

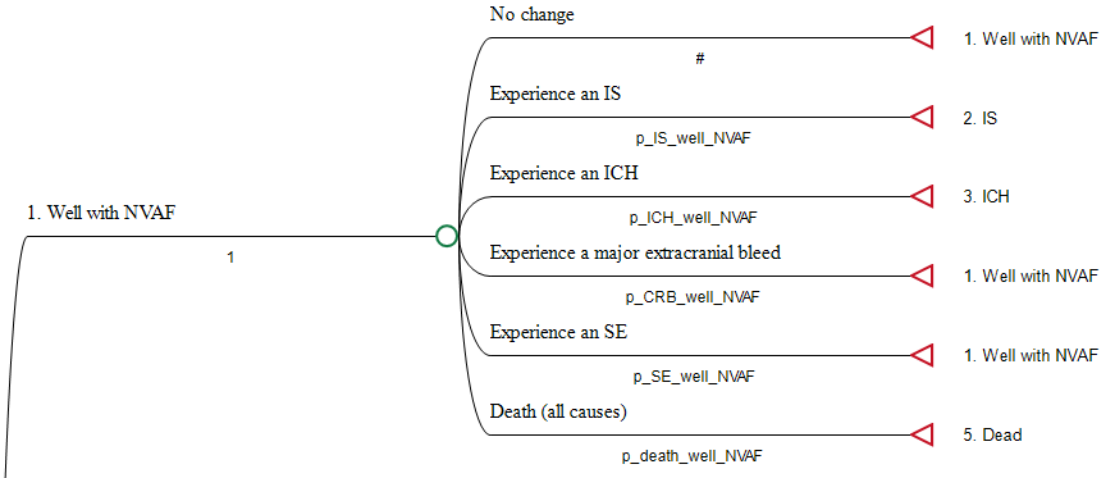
Patients experiencing IS despite OAC may be at particularly high risk of future IS. Recent analysis of pooled individual patient data from an international collaboration of prospective cohort studies found that the rate of recurrent IS was twice as high in patients who had had their index stroke despite taking an anticoagulant, compared to those who were not on anticoagulation at the time of the index stroke.[163] Although they have been excluded from RCTs, AF patients with ICH are at very high risk of subsequent IS.[86]

Stroke (ischaemic or haemorrhagic) may also have a sustained impact on patient QoL. Five-year follow-up of stroke patients treated at one of 4 European rehabilitation centres in Belgium, Germany, Switzerland or the UK found that a significant portion (40%) of the study cohort reported HRQoL below population norms.[164]

8.2.4.2 Clinical events

The 6 events or transition states comprised: no event, IS, ICH, major extracranial bleed, SE and death (all-cause). In each cycle, and from any non-dead health state, a patient could experience any one of the clinical events or no event. An example of the transitions possible from the 'well with NVAF state' is provided in ***Figure 36.*** The same transitions are possible from all other non-dead states. Death is an absorbing state from which no further transitions are possible.

Figure 36 Example of the transition states possible from any health state



Abbreviations:
ICH: intracranial haemorrhage; **IS**: ischaemic stroke; **NVAF**: nonvalvular atrial fibrillation; **SE**: systemic embolism.

8.2.4.3 Modelling features and specifications

To capture in full the differences in costs and effects between DOACs and VKAs, a lifetime horizon was adopted. In line with the *López-López model* and several other previous models, a 3-month cycle length was adopted. The model design allows patients to experience only one clinical event each cycle. Although not impossible, it is rare for a patient to experience 2 events within the space of 3 months.[155]

The cost-effectiveness of apixaban, dabigatran, edoxaban and rivaroxaban against a common comparator (VKAs) in separate pairwise comparisons were evaluated. Intra-class comparisons between DOACs were not made.

For each DOAC, standard daily doses as defined in the ESC guidelines were considered (i.e. apixaban 5 mg twice daily, dabigatran 150 mg twice daily, edoxaban 60 mg once daily, and rivaroxaban 20 mg once daily).[86] A reduced dose of dabigatran (110 mg twice daily) is recommend for all patients 80 years of age or older[86] so a reduced dose of dabigatran was considered in a scenario analysis.

VKAs were treated as a drug class in accordance with the clinical section of the HTA. VKA treatment with a target INR of 2.0–3.0, as recommended by ESC guidelines, was assumed.[86] The VKAs relevant to the Swiss context are acenocoumarol and phenprocoumon, but there is limited RCT evidence for these drugs. There is, however, a large RCT evidence-base for warfarin, the most prescribed VKA worldwide. This HTA has assumed that warfarin is substantially equivalent to phenprocoumon and acenocoumarol. An average cost across phenprocoumon and acenocoumarol was used, based on Swiss utilisation data.

Incorporating results from the clinical evidence evaluation, the transition of a hypothetical cohort of patients through the included health states and events was modelled. Costs and utilities were assigned

to the modelled heath states and events, allowing us to assess the incremental costs, incremental effects (measured using QALYs) and incremental cost effectiveness ratio (ICER) of each DOAC vs VKAs.

8.2.4.4 Model assumptions

A summary of model assumptions is provided in ***Table 125***, ***Appendix D***.

Firstly, it was assumed that patients do not stop or change type of OAC after an IS. ESC guidelines recommend long-term secondary prevention of stroke using OAC in AF patients with IS or TIA (Class I recommendation).[86] A recent analysis of pooled individual patient data from an established international collaboration of prospective cohort studies found that, among patients who had IS despite taking an anticoagulant, changing the type of anticoagulant after the index IS event was not associated with a decreased risk of future IS.[163] Robust data to inform the optimal timing of treatment re-initiation are lacking; however, ESC guidelines note that from a cardiological perspective, OAC should be reinitiated as soon as possible (generally, within the first 2 weeks).[86]

Secondly, it was assumed that patients reinstate their initially-assigned OAC after an ICH.[44,158] ESC guidelines recommend that for AF patients at high risk of IS, re-initiation of OAC should be considered in consultation with a neurologist/stroke specialist after a trauma-related ICH or acute spontaneous ICH, following careful consideration of risk and benefits.[86] However, this ESC recommendation is based on level C evidence, and the guideline itself indicates that there is a reluctance among clinicians to reinitiate OAC in AF patients who survive ICH.[86] In a pooled analysis of 2 UK cohorts of patients with first-ever ICH, the percentage of patients with AF treated with OAC dropped from 57.1% before the index ICH to 6.0% after the index ICH.[165] A structural sensitivity analysis, in which patients were assumed to stop OAC after an ICH, was also included.

Thirdly, it was implicitly assumed that treatment compliance within the hypothetical model cohort (and within the Swiss population, by extension) was aligned with patient compliance within the included RCTs. Further adjustments for treatment discontinuations were not incorporated in the model structure.

8.2.5 Economic model: inputs

8.2.5.1 Transition probabilities

8.2.5.1.1 Applicability of the evidence

This section addresses how the characteristics of the hypothetical model cohort compare with circumstances of use in Switzerland. Clinical evidence informing the baseline transitions was sourced from a meta-analysis of RCTs, which included 94,656 patients from 23 RCTs.[44] Patient characteristics

of the hypothetical model cohort were assumed to align with those of patients included in the meta-analysis.

To consider applicability to the Swiss context, pooled demographic data from 2 Swiss AF cohorts (the BEAT-AF and Swiss-AF cohorts) were considered. The pooled demographic data were summarised previously (***Section 7.2.5.1***); some of which is repeated below (***Table 19***).Overall, around 84.2% of the combined cohort were taking an OAC (58% VKA; 42% DOAC); therefore, this cohort provides a good representation of treated AF patients.[166] An additional publication was identified to provide details on the quality of VKA therapy in Switzerland. This cohort included 332 patients who had been seen in a single Swiss cardiology centre and who were in a chronic state of VKA anticoagulation (target INR: 2.0–3.0).[167]

Table 19 provides a comparison between patient characteristics across the RCTs included in the *López-López* meta-analysis and circumstances of use in Switzerland.

Table 19 Comparison of patient characteristics between RCTs informing the baseline transitions and Swiss patients

Parameter	RCT populations informing baseline transitions [a]	Swiss patients
Patient characteristics		
Age	70 years (range 63.6 to 81. 5)	Mean age ± SD: 72±10 years
Gender	63.3% male (range 44.9 to 82.9%)	70.4% male.
BMI	28.0 kg/m^2 (range 24.4 to 30.5)	Mean BMI ± SD: 27.4 ± 4.8
Previous stroke (%)	20.2% (range 5.0 to 63.8%)	18.0% had a history of stroke or TIA.
Hypertension (%)	73.8% (range 38.0 to 93.7%)	69.2% with hypertension
Chronic heart failure (%)	32 % (range 0 to 100%)	22.9% with history of congestive heart failure
Quality of INR control		
Mean TTR (VKA)	63.8% (range 45.1 to 83.0%)	In a Swiss cohort of 332 patients in a state of chronic VKA therapy, median TTR was 69% (IQR: 51 to 89%).

Abbreviations:
BMI: body mass index; **INR**: international normalised ratio; **IQR**: interquartile range; **NMA**: network meta-analysis; **OAC**: oral anticoagulant; **SD**: standard deviation; **TIA**: transient ischaemic attack; **TTR**: time in therapeutic range; **VKA**: vitamin K antagonist.
Notes:
[a] Demographic data for the hypothetical model cohort were extracted from Walter et al 2021.[100] Data pertains to the López-López network meta-analysis cohort.[44] Data ranges for mean age, mean BMI and mean TTR reflect ranges in mean age, BMI and TTR across the included RCTs. Data ranges for percentage male gender and percentage with previous stroke, hypertension or chronic heart failure reflect variability in these proportions across the included RCTs.[44,158]

At face value, time in therapeutic range (TTR) appears to be improved in Swiss patients relative to RCT cohorts (***see Table 19***), although this is difficult to assess given variability in the mean TTR across the included RCTs (range: 45.1 to 83.0%, median 62.2%, ***Table 19***).

8.2.5.1.2 Baseline transitions

The *López-López model* relied upon evidence from the warfarin arms of included RCTs to inform the transition probabilities for patients on VKA.[158] The hazards of events with VKAs were estimated using a competing risks single-treatment meta-analysis.[158,159]

The hazards from the *López-López model* were used to inform the transitions probabilities for patients receiving VKA in the model for this HTA (***Table 20***). Patients in the included RCTs shared similar demographics to the target population for this HTA (see ***Table 19***) and the hazards reflect event risks specifically for patients receiving VKA.

Annual hazards were converted into 3-month probabilities using the formula $1\text{-EXP}\left(-r \times \frac{1}{4}\right)$. Beta distributions were used to reflect uncertainty in the annual rates for the PSA.

Table 20 Annual hazard of events for patients treated with VKA

Event	Annual hazard	Event	Annual hazard
All-cause mortality	0.038 (0.028 to 0.052)	Major/clinically-relevant extracranial bleed	0.066 (0.031 to 0.13)
ICH	0.0094 (0.0057 to 0.017)	SE	0.017 (0.0059 to 0.041)
IS	0.012 (0.01 to 0.013)		

Abbreviations:
ICH: intracranial haemorrhage; **IS**: ischaemic stroke; **SE**: systemic embolism; **VKA**: vitamin K antagonist.
Notes:
Annual hazards of events for the RCT population are reported as mean (95% confidence intervals).
Source:
López-López model and Austrian adaptation.[44,100,158]

8.2.5.1.3 Relative treatment effects of direct oral anticoagulants

8.2.5.1.3.1 Effect estimates informed by RCT evidence

Transition probabilities for patients receiving DOAC were derived using estimates of relative treatment effect for each DOAC relative to VKAs. Estimates of treatment effect reflect those reported in the clinical section of this HTA (***Section 7.2.4***). Effect estimates informed by the RCT evidence were reported as RRs in comparison to VKA (***Table 21***). It was assumed that the RR between the intervention and comparator would remain constant across the duration of therapy.

To compute transition probabilities, annual hazards of each clinical event for patients treated with VKA were multiplied by the estimates of relative treatment effect, then converted into 3-month probabilities.[168] Log normal distributions were used to reflect uncertainty in the RRs for the PSA.[169]

Table 21 RCT-based estimates of relative treatment effect used in the model

Clinical event	Apixaban 5 mg	Dabigatran 150 mg	Edoxaban 60 mg	Rivaroxaban 20 mg
IS	0.92 (0.75 to 1.14)	0.77 (0.61 to 0.99)	1.00 (0.84 to 1.20)	0.93 (0.74 to 1.16)
SE [a]	0.54 (0.12 to 2.44)	0.91 (0.74 to 1.10)	0.81 (0.46 to 1.44)	0.88 (0.75 to 1.03)
ICH	0.42 (0.31 to 0.59)	0.41 (0.28 to 0.60)	0.46 (0.34 to 0.62)	0.66 (0.47 to 0.92)
Major bleed [b]	0.70 (0.61 to 0.81)	0.94 (0.82 to 1.07)	0.80 (0.71 to 0.91)	1.03 (0.89 to 1.18)
All-cause mortality	0.90 (0.81 to 1.00)	0.89 (0.79 to 1.01)	0.92 (0.84 to 1.01)	0.92 (0.83 to 1.03)

Abbreviations:
ICH: intracranial haemorrhage; **IS**: ischaemic stroke; **SE**: systemic embolism.
Notes:
Results are reported as RRs and 95% CI.
[a] The effect estimate for the combined outcome of stroke or SE was used as a proxy to reflect the relative impact of DOACs on the occurrence of SE in the model.
[b] The relative treatment effect for major/life-threatening bleeding was used to reflect the relative effect of DOACs on the occurrence of extracranial bleed events in the model.

8.2.5.1.3.2 Effect estimates informed by NRSI evidence

Effect estimates for each DOAC relative to VKAs derived from NRSIs were reported as hazard ratios (HRs) with 95% CIs (see ***Table 22***). The NRSI-based RRs reported in ***Section 7.2.4*** were not used because of a high risk of confounding in these effect estimates. Annual hazards of each clinical event for patients treated with VKA were multiplied by the estimates of relative treatment effect, then converted into 3-month probabilities. Log normal distributions were used to reflect uncertainty in HRs for the PSA.[169]

The NRSI data reflect comparisons between DOACs and VKAs reimbursed in Switzerland (phenprocoumon and acenocoumarol). Moreover, these data capture the relative effect of each DOAC (vs VKAs) in the real-world setting, where patient compliance may differ to that observed within the RCT context. Limited data pertaining to edoxaban were available; therefore, an NRSI-based analysis could not be undertaken for this DOAC.

Table 22 NRSI-based estimates of relative treatment effect used in the model

Clinical event	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
IS	1.21 (0.89 to 1.66)	1.14 (0.80 to 1.64)	0.88 (0.74 to 1.05)	1.04 (0.96 to 1.14)
SE [a]	0.83 (0.58 to 1.19)	0.89 (0.78 to 1.03)	0.61 (0.15 to 2.57)	0.95 (0.78 to 1.15)
ICH	0.55 (0.42 to 0.72)	0.52 (0.36 to 0.73)	No data	0.69 (0.58 to 0.81)
Major bleed [b]	0.63 (0.52 to 0.75)	0.75 (0.61 to 0.92)	No data	1.08 (1.03 to 1.13)
All-cause mortality	1.16 (0.88 to 1.54)	1.00 (0.92 to 1.09)	1.40 (1.22 to 1.61)	1.18 (1.05 to 1.33)

Abbreviations:
ICH: intracranial haemorrhage; **IS**: ischaemic stroke; **NRSI**: non-randomised studies of intervention; **SE**: systemic embolism.
Notes:
Results are reported as HR and 95% CI.
[a] The effect estimate for the combined outcome of stroke or SE was used as a proxy to reflect the relative impact of DOACs on the occurrence of SE in the model.
[b] The relative treatment effect for major/life-threatening bleeding was used to reflect the relative effect of DOACs on the occurrence of extracranial bleed events in the model.

8.2.5.1.4 Age-based adjustments for all-cause mortality

Mortality was modelled per the approach used in the *López-López model*.[44,158] The annual hazard for all-cause mortality detailed in ***Table 20*** (i.e. annual hazard of 0.038 for patients on VKA) was assumed representative of the hazard of death for a 70-year-old NVAF population (60% male) on VKA. This was adjusted for each age group less than or greater than 70 years (5-yearly intervals) by multiplying the annual hazard (0.038) by the ratio between the hazards of death in the general population for the age group of interest relative to the 70–74-year-old group. The resulting annual hazards for each age group are shown below (***Table 23***). Annual hazards were converted into 3-month probabilities of death (all-cause). For patients treated with DOAC rather than VKA, the relevant annual hazard of death was first multiplied by the estimated relative treatment effect, then converted into a 3-month probability of death (all-cause). The effect of treatment on all-cause mortality was assumed constant across age groups.

Table 23 Age-based annual hazards of all-cause death

Age group	Annual hazard	Age group	Annual hazard
60 to 65 years	0.014	70 to 79 years	0.062
65 to 69 years	0.023	80 to 85 years	0.126
70 to 75 years	0.038	85+ years	0.378

Source:
Calculations made as part of this economic evaluation.

8.2.5.1.5 Adjustment for the impact of prior events

Adjustments for the risk of prior IS or ICH on the risk of future clinical events were made as per the approach used in the *López-López model*.[44,158]

The effects of prior IS or ICH on the risk of future stroke, SE and bleed events were derived from analyses on the Swedish AF cohort.[44,170] This cohort comprised 182,678 Swedish patients with a diagnosis of AF who were followed for an average of 1.5 years. Analyses informing the *López-López model* estimates had been performed on data from a subset of 90,490 patients without anticoagulation treatment.[44,170] The effect of prior stroke on the future risk of death (all-cause) was derived from analyses on patients included in a nationwide Danish registry of all hospitalised stroke patients in Denmark with IS and AF.[171] It was assumed that ICH would have the same effect on future risk of death as a stroke.

Inputs were sourced directly from the *López-López model,* which expressed the effect of prior events on future risk as log-HRs.[44,158] The model for this HTA first calculated the exponential of the log-HR and then multiplied the exponent by the annual hazard of the event for a patient treated with VKA and by any relevant estimates of relative treatment effect. Finally, 3-month probabilities were derived. Normal distributions were used to reflect uncertainty in the log-HRs for the PSA.[44,158]

The effects of prior IS and ICH on future risk were assumed to be multiplicative. Thus, patients with a history of both IS and ICH were at a heightened risk of future events compared to patients with a history of either IS or ICH alone.

Table 24 Log-HR (standard error) for the effect of previous events on future risk

Event	Future IS	Future SE	Future ICH	Future bleed	Future death
IS	1.39 (0.03)	1.28 (0.02)	0.49 (0.09)	0.33 (0.05)	0.28 (0.15)
ICH	0.58 (0.07)	0.60 (0.06)	2.32 (0.09)	1.08 (0.07)	0.28 (0.15)

Abbreviations:
HR: hazard ratio; **ICH**: intracranial haemorrhage; **IS**: ischaemic stroke; **SE**: systemic embolism
Notes:
Reported as log-HR (standard error)
Source:
López-López model[44,158]

8.2.5.2 Health state utilities

Utilities are a measure of preference between health states. The utility and disutility values used in the economic model are summarised below (***Table 25***).

The health state utility for patients with NVAF was informed by a Swiss cohort of 2,412 patients with AF (detailed in ***Section 8.2.5.2.1***).[172] Of the 2,412 patients, 90.4% were taking an OAC at the time of EQ-5D (EuroQol 5-dimension questionnaire) assessment (51.0% taking DOAC; 39.4% VKA), therefore this cohort was considered a reasonable representation of the hypothetical model cohort, who were all receiving OAC.

The remaining heath state utilities and the disutility associated with acute events were informed by those used in the *López-López model,* although health state utilities were adjusted in accordance with the higher baseline utility reported for Swiss patients (detailed in ***Section 8.2.5.2.2***). Moreover, for this HTA the same post-event utility was assumed following an ischaemic or haemorrhagic stroke, or other ICH (detailed in ***Section 8.2.5.2.2***). Regarding the disutility associated with acute events (detailed in ***Section 8.2.5.2.3***), it was assumed that the values used in the *López-López model* could be applied to the Swiss population. Disutilities due to clinical events were assumed to last for one model cycle (i.e. 3 months).

The health state utilities shown in ***Table 25*** were divided by 4 to derive the relevant QALY payoff per 3-month cycle. For patients with a history of multiple events (i.e. IS and ICH), health state utilities were assumed to be multiplicative. Normal or uniform distributions were used to capture uncertainty in the utility and disutility parameters for the PSA.[44,158]

Table 25 Utility and disutility inputs

Health state	Utility	Clinical event	Disutility
Well with NVAF	0.820 (0.813 to 0.827)	Acute IS	–0.590 (–0.885 to –0.295)
History of IS	0.731 (0.691 to 0.771)	Acute ICH	–0.179 (–0.304 to –0.054)
History of ICH	0.731 (0.691 to 0.771)	Major bleed	–0.030 (–0.033 to –0.027)
		SE	–0.131 (–0.197 to –0.066)

Abbreviations:
ICH: intracranial bleed; **IS**: ischaemic stroke; **NVAF**: nonvalvular atrial fibrillation; **SE**: systemic embolism
Notes:
Utilities and disutility inputs are reported as means along with the lower and upper bounds used in sensitivity analysis.

8.2.5.2.1 Baseline utility

The baseline utility for patients with NVAF in the *López-López model* was sourced from a study of a cohort of 5,050 European patients with AF enrolled in 2003–2004 at 182 outpatient cardiology clinics or specialised hospital departments across 35 European countries (reflecting 95% of the Euro heart survey cohort).[44,173,174] EQ-5D responses were translated into utilities via an algorithm developed for general population preferences in the UK. Mean health utility per patient at baseline was 0.751 (SD 0.269, n = 5,050) compared to 0.779 (SD 0.253, n = 3,045) at one-year follow-up.[173] The *López-López model* assumed a baseline utility of 0.779 for its model cohort.[44,158]

Among a cohort of 2,412 Swiss patients with AF age ≥65 years enrolled between April 2014 and August 2017 from 13 clinical centres in Switzerland (reflecting 99.9% of the Swiss-AF cohort), the mean health utility at baseline, valued using the European value set, given an absence of a Swiss-specific set, was 0.82 (SD 0.17; n = 2,412).[172] In comparison to the European cohort, the Swiss cohort of patients with AF reported a higher utility score. The mean age of the Swiss cohort was higher (73.2 vs 66.4 years) and a higher proportion of the study cohort was male (72.6% vs 58.1%).

Given the Swiss context of this evaluation, the baseline Swiss-AF cohort mean utility value as the health state utility for the 'well with NVAF' state was adopted in the model (***Table 25***).

8.2.5.2.2 History of stroke or intracranial haemorrhage

In the Swiss-AF cohort, history of stroke was not a significant predictor of EQ-5D utility; however, in the Euro heart survey a history of stroke (at baseline) was associated with reduced EQ-5D utility at both baseline and one-year follow-up.[172,173] The occurrence of stroke during the one-year follow-up period had a large negative effect on EQ-5D utility.[173] The model for this HTA assumed that histories of IS and/or ICH are associated with long-term reductions in HRQoL, relative to NVAF patients without a history of these events.

In the *López-López model*, HRQoL estimates for patients with a history of IS and/or ICH were sourced from a German cohort of 77 patients who completed the EQ-5D survey 4 years after a stroke event.[175]

Health state utilities for the post-event states were based on those used in the *López-López model*, although these were adjusted to account for the higher base utility of the Swiss (relative to European) cohort and the same long-term disutility after stroke was assumed, irrespective of whether it was due to ischaemic or haemorrhagic causes.[164,173] Five-year follow-up of stroke survivors treated at one of 4 European rehabilitation centres found that being treated in a Swiss centre vs another centre (Belgian, German or UK) was positively associated with HRQoL.[164] Thus, it was assumed in this HTA that the higher HRQoL for Swiss (relative to European) stroke survivors may persist to long-term follow-up. In this same study, the type of stroke (ischaemic vs haemorrhagic) did not show an association with HRQoL at 5 years.[164] Thus, for this HTA the same health state utility was assumed for IS and ICH states.

8.2.5.2.3 Disutility due to acute events

Disutility values associated with acute clinical events were obtained directly from the *López-López model* (***Table 25***).[44,158] Thus, it was implicitly assumed that adverse health events would negatively affect the HRQoL of patients in a similar way across Swiss and UK contexts during their acute phase.

8.2.5.3 Costs

Costs, from the perspective of the healthcare payer, were estimated for the following: DOAC and VKA medication and monitoring costs; clinical event costs for IS, SE, ICH and major extracranial bleeds.

8.2.5.3.1 Medication costs

8.2.5.3.1.1 Vitamin K antagonists

For the prevention of thromboembolic events in AF, a target INR of 2.0–3.0 is recommended.[86] Dose-response can vary between patients (interindividual variability) and over time within one patient (intraindividual variability).[32] Thus, the dose required to maintain target INR can vary both between patients and for a single patient over time.

For acenocoumarol, the maintenance dose is usually between 1 and 8 mg daily, and for phenprocoumon, between 1.5 and 4.5 mg daily.[176] Among 1,095 patients visiting one of 2 Dutch anticoagulation clinics receiving either acenocoumarol (n = 471) or phenprocoumon (n = 624) with a target INR of 2.0–3.5, the median (2.5 to 97.5th percentile) maintenance doses (mg/day) were 2.34 (1.00 to 5.00) mg/day and 2.12 (0.83 to 4.27) mg/day, respectively.[177] Data on the average maintenance dose among Swiss-specific cohorts were not identified.

Base case daily costs for phenprocoumon and acenocoumarol were derived assuming a daily dose of 2.12 mg and 2.34 mg, respectively (***Table 26***). Ranges were informed by the doses detailed in the product information sheets for each drug.[176] Triangular distributions were used to capture uncertainty in

the daily doses for the PSA. Costs per day were estimated according to the most frequently sold pack sizes:

- Phenprocoumon: 100 pack of 3-mg tablets at a cost of CHF19.20
- Acenocoumarol: 100 pack of 1-mg tablets at a cost of CHF7.20.

When estimating the daily drug costs for the VKA arm, a weighted average cost across phenprocoumon and acenocoumarol was derived based on Swiss utilisation data. Specifically, the use of acenocoumarol vs phenprocoumon was weighted according to the prescribing patterns of Swiss clinicians over the last 3 years, informed by IQVIA survey data.[178]

Table 26 Estimated daily drug costs for VKA

Active substance	Dose per day (mg)	Estimated cost per day (CHF)	Market share (%)
Acenocoumarol	2.34 (range: 1 to 8)	0.17 (0.07 to 0.58)	25.9
Phenprocoumon	2.12 (range: 1.5 to 4.5)	0.14 (0.10 to 0.29)	74.1

Abbreviations:
CHF: Swiss francs.

8.2.5.3.1.2 Direct oral anticoagulants

Daily costs for each DOAC were estimates according to the standard doses outlined in ESC guidelines.[86] Daily costs (***Table 27***) were derived as an average across available pack sizes, weighted based on the quantity of packs sold in 2021. Ranges were based on the cheapest and most expensive pack sizes available. Triangular distributions were used to capture variability in the daily cost of each DOAC for the PSA.

Table 27 Estimated daily drug costs for DOAC

Active substance	Dose per day	Cost per day (CHF)
Apixaban	10 mg (i.e. 5 mg twice daily)	3.01 (2.88 to 3.27)
Dabigatran	300 mg (i.e. 150 mg twice daily)	3.07 (2.85 to 3.22)
Edoxaban	60 mg (i.e. 60 mg once daily)	2.79 (2.79 to 3.21)
Rivaroxaban	20 mg (i.e. 20 mg once daily)	2.94 (2.87 to 3.81)

Abbreviations:
CHF: Swiss francs; **DOAC**: direct oral anticoagulant.
Note:
Audience award prices were used in the derivation of daily costs.

8.2.5.3.2 Monitoring costs

8.2.5.3.2.1 Vitamin K antagonists

The quality of care for VKAs depends upon the time during which a patient's INR is within therapeutic range. For the prevention of thromboembolic events in AF, it is recommended that individual TTR should be 70% or more.[86] Dose–response can vary between patients and over time within one patient, therefore frequent monitoring of anticoagulant effect is required.[32] Treatment is typically managed by a GP, in hospital, or in specialised anticoagulation clinics in some countries (e.g. Spain and the Netherlands).[32] In Switzerland, there are no specialised anticoagulation clinics and INR measurements and VKA dose prescriptions are generally performed by GPs.[167] In the model, it was assumed that all INR testing would be performed by a GP.

In a Swiss cohort of 332 patients with NVAF in a chronic state of VKA anticoagulation (62% male, mean age 74 ± 9 years), the median interval between INR measurements was 20 days (interquartile range [IQR]: 13 to 27).[167] In the model, the number of INR tests required per 3-month cycle was derived assuming an average interval of 20 days between each test. Product information sheets for acenocoumarol and phenprocoumon recommend regular INR monitoring at least once a month (or every 4 weeks);[176] therefore, an upper bound of 30 days between INR measurements (i.e. once a month) was used. A lower bound of 15 days (i.e. twice a month) was, arbitrarily, assumed. A uniform distribution was used to capture variability in the INR monitoring interval for the PSA.

The number of tax points per episode was derived using TARMED and Analysenliste positions and valued using the median Swiss cantonal tax point value for 2022 (CHF0.9 per tax point).[179]

Table 28 Input parameters used in deriving monitoring costs associated with VKAs

Input	Value	Comments
Days between INR tests	20 (15 to 30) days	
Unit cost for GP visit (10 min consult, including blood collection)	42.29 CHF	TARMED positions 00.0010, 0.0015, 00.0030, 00.0710, and 00.0715
Unit cost for analysis of INR	12.30 CHF	Analysenliste positions: 1700.00 or 1700.01 (weighted average based on 2020 claims numbers [3.5% for 1700.00 and 96.5% for 1700.01]). Auftragstaxe of CHF21.60 for INR analyses done in contract laboratories [a]

Abbreviations:
CHF: Swiss franc; **GP**: general practitioner; **INR**: international normalised ratio.
Notes:
[a] The value of the 'auftragstaxe" in Swiss francs is based on expert opinion. This value was only included for the proportion of INR tests claimed via Analysenliste position 1700.00 (i.e. 3.5% of tests).
One tax point was assumed to have a value of CHF0.9, equal to the median of the Swiss cantonal tax point values for 2022.[179]

At a high level, many of the assumptions appear consistent across the existing Swiss evaluation and the model for this HTA. Notably, the existing evaluation assumed one INR test every 3 to 4 weeks during the maintenance phase and included a 10-minute consult with a doctor as part of INR testing.[140] However, the unit cost used in the prior evaluation (CHF23 per test) was lower than that derived as part of the present cost analysis.

At-home INR self-testing could potentially reduce the cost and the intensity of clinician involvement in VKA therapy, but it is unclear how effective these tests are, how much they cost, or how widely available they are in Switzerland; therefore, they were not included in the economic evaluation.

8.2.5.3.2.2 Direct oral anticoagulants

For patients treated with DOAC, 2–3 GP visits per annum were costed, using the same unit cost as described above (***Table 28***). A uniform distribution was used to capture variability in the frequency of GP monitoring for the PSA.

8.2.5.3.3 Acute event costs

The unit costs associated with the clinical events included in the model are summarised in ***Table 29***, and further detailed in the subsequent sections (***Section 8.2.5.3.3.1***, ***Section 8.2.5.3.3.1.2*** and ***8.2.5.3.3.2***). Costs associated with the incidence of acute stroke or bleed events were estimated according to Swiss DRGs.[180] Costs associated with acute SE events were derived based on average Swiss inpatient length of stay (LOS) data for ICD-10 code I74.[181] Only for stroke events were additional costs associated with rehabilitation considered. These costs were informed by length of inpatient rehabilitation stay data from a Swiss cohort and daily rehabilitation costs informed by inpatient rehabilitation tariffs.[182,183] Triangular distributions were used to reflect uncertainty in acute event costs for the PSA.

Table 29 Unit costs associated with the modelled clinical events

Event	Unit cost (CHF)	Source	Comments
Stroke	21,386.35 (9,927.30 to 46,224.25)	DRG codes B39A–C and B70A–G[180]	These DRG codes apply to both IS and ICH (ICD-10 codes I60 to I64)
Rehabilitation post-stroke	46,124.40 (25,478.24 to 67,649.12) [a]	RCG codes TR13A–C[183] LOS data from a Swiss cohort of 135 stroke patients[182]	Rehabilitation costs were assumed to be incurred by 45.0% of the cohort (range: 40.8 to 49.2%)[184,185]
Additional post-stroke costs (scenario analysis only)	30,516.86 [b]	Derived from acute hospitalisation and inpatient rehabilitation costs	In the Swiss costing study, acute hospitalisation and inpatient rehabilitation accounted for 58% of total costs in the first year after stroke.[184]
Major bleed	10,515.73 (5,471.00 to 16,525.05)	DRG codes G67A–D[180]	Limited to GI bleeds

Event	Unit cost (CHF)	Source	Comments
SE	23,395.02 (10,424.96 to 33,229.56)	LOS data for hospital episodes with a main diagnosis coded as ICD-10 I74.[181] Multiplied by average cost per day of inpatient care.[186]	Average (weighted) LOS was 8.98 days. Average cost for a day's hospitalisation in acute care in 2020 was CHF 2,506 [c]

Abbreviations:
CHF: Swiss franc; **DRG**: diagnosis-related group; **GI**: gastrointestinal; **ICD-10**: International Classification of Diseases, 10th revision; **ICH**: intracranial haemorrhage; **IS**: ischaemic stroke; **LOS**: length of stay; **RCG**: rehabilitation cost groups.
Notes:
[a] calculated as 1.156 × CHF760/day × 52.5 days. For the lower and upper bound estimates, number of days used in the calculation was 22 and 77 days, respectively.
[b] calculated as [(CHF21,386.35 + (CHF 46,124.40 × 0.450)] × (42/58)
[c] over the period December 2020 to June 2022, there was minimal change in the price of inpatient hospital services; therefore, no adjustment was made.[187]

8.2.5.3.3.1 Ischaemic stroke and intracranial haemorrhage

IS and ICH event costs used in the model included costs for both the inpatient acute hospital episode and the cost of rehabilitation following discharge for a proportion of patients. Strokes were limited to non-fatal events given all-cause mortality was included as a distinct event in the model.

8.2.5.3.3.1.1 Hospitalisation costs

DRG codes B39A–C and B70A–G were identified as relevant for non-fatal stroke events with more than one day's occupancy, without differentiating between ischaemic and haemorrhagic origins. Whilst not all intracranial bleeds are classified as haemorrhagic strokes, the simplifying assumption was made that all intracranial bleeds would result in costs and HRQoL decrements equivalent to that of haemorrhagic stroke events. In a cohort of 567 Swiss stroke inpatients treated in 2014, the minimum length of hospital stay was 2 days;[188] therefore, DRG codes for episodes of one day's occupancy were excluding from costing calculations.

The average (simple) cost for the identified DRG codes was CHF21,386.35 (range: CHF9,927.00 to CHF46,224.25), with an average LOS of 8.33 days (see ***Table 128*** in ***Appendix D***).

ICD-10 codes I60 to I62 for ICH, I63 for IS and I64 for unspecified stroke (i.e. not referred to as bleeding or infarct) were identified as relevant to stroke events.[189,190] Analysis of LOS data from the Medical Statistics of Hospitals (Medizinische Statistik der Krankenhäuser) 2021, showed a weighted average LOS across ICD-10 codes I60 to I64 of 15.1 days.[181] According to Swiss Health Pocket Statistics, the average daily cost per patient for a day's hospitalisation in acute care in 2020 was CHF2,506.[186] Multiplying the average LOS by this daily cost gives a cost per episode of CHF37,840.60, which falls within the range used for the acute cost of hospitalisation. Over the period December 2020 to June 2022, there was minimal change in the price of inpatient hospital services; therefore, no adjustment was made when converting to a 2022 costing year.[187]

8.2.5.3.3.1.2 Inpatient rehabilitation costs

Rehabilitation cost groups (RCGs) TR13A–C were identified as relevant for inpatient rehabilitation episodes following a stroke. These codes have daily costs weights of 1.348, 1.114 and 1.007, respectively (average 1.156), which were multiplied by a base price of CHF760.[183]

The assumed length of inpatient rehabilitation was informed by the median LOS among 135 stroke patients treated at a single Swiss rehabilitation centre between March 2002 and September 2004 (median: 52.5 days; IQR: 29 to 77).[182] IQR was used in deriving the lower and upper unit cost estimates for rehabilitation for sensitivity analysis (***Table 29***). In a cost analysis of 131 patients with acute stroke treated in a single Swiss hospital between January 2002 and March 2003, a LOS of 39 days for inpatient rehabilitation was reported.[184]

Only a percentage of the cohort was assumed to require inpatient rehabilitation following a stroke or other ICH. In the cost analysis described above, 58 patients required inpatient rehabilitation, equating to 49.2% of the 118 patients surviving beyond the acute hospital phase.[184] Among a Swiss population telephone survey (July 2004 to January 2005) of a sample of 509 individuals who had cared for someone with stroke, 387 patients recalled acute inpatient care while 158 recalled inpatient rehabilitation following an acute inpatient episode (40.8% of the 387 treated as inpatients).[185] The model for this HTA assumed that 45.0% (range: 40.8 to 49.2%; uniform distribution) of patients would require inpatient rehabilitation after a stroke or other ICH.

8.2.5.3.3.1.3 Outpatient costs

Although a cost estimate based on LOS in inpatient facilities (as used in this HTA) does not consider direct costs such as GP visits, physiotherapy, occupational therapy etc., it is still a meaningful method of cost analysis, particularly for cerebrovascular accidents for which inpatient care generates a high proportion of total costs.[185] Nevertheless, a Swiss cost analysis found acute hospitalisation and inpatient rehabilitation to account for only 58% of total costs in the first year after stroke; a lower proportion than reported elsewhere.[184] In scenario analysis, acute event costs for IS and ICH events were increased to capture additional outpatient cost components.

8.2.5.3.3.2 Major/clinically-relevant bleeds

GI bleeding is a well-known complication of OAC.[4] For the costing of this event, DRG codes G67A–D were considered. The average (simple) cost for the identified DRG codes was CHF10,515.73 (range: CHF5,471 to CHF16,525.05) with an average LOS of 6.9 days (***Table 129*** in ***Appendix D***).

ICD-10 codes K92.2, K62.5, K55.22, R04.x, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.4, K27.6, K28.0, K28.2, K28.4 and K28.6 were identified as relevant, in line with codes used

by Mueller et al 2018.[3] The weighted LOS for these codes was 6.36 days, equating to a cost of CHF15,938.16 multiplied by the average cost per day of inpatient care in Switzerland,[186,187] which is within the range used for the acute cost of bleed events.

8.2.5.3.3.3 Systemic embolism

Treatment for SE was costed as an inpatient event. In an analysis of 221 validated extracranial systemic embolic events occurring in 219 of 37,973 RCT patients, medical care involved clinical assessment only in 5%, hospitalisation without procedural intervention in 31%, hospitalisation with surgical or endovascular procedures in 60% and amputation in 4%.[191]

ICD-10 codes I74 (arterial embolism and thrombosis) were identified as relevant for systemic arterial embolism. Weighted average LOS for these entries was 8.98 days, equating to a cost of CHF22,503.88 when multiplied by the average cost per day of inpatient care in Switzerland.[186,187] Low and high LOS were 4.0 and 12.75, equating to costs of CHF10,424.96 and CHF33,229.56, respectively.

8.2.6 Findings cost-effectiveness

8.2.6.1 Apixaban vs VKA

8.2.6.1.1 ICER

The expected costs (disaggregated) of apixaban vs VKAs are presented in ***Table 30***. Apixaban was more expensive in terms of drug costs than VKAs; however, it was cost-saving in terms of monitoring costs and clinical event costs (***Table 30***). Overall, apixaban was cost-saving in comparison to VKAs.

Table 30 Disaggregated costs of apixaban vs VKA

Cost Component	Expected costs with apixaban (CHF)	Expected costs with VKA (CHF)	Incremental cost (CHF)
Drug costs	10,097.09	461.95	9,653.14
Monitoring costs	985.16	8,745.48	–7,760.32
Clinical event costs	14,773.77	22,943.65	–8,169.88
TOTAL	25,856.02	32,151.08	–6,295.06

Abbreviations:
CHF: Swiss francs; **VKA**: vitamin K antagonist.

The expected outcomes of apixaban vs VKAs are presented in ***Table 31***. Apixaban was associated with greater life years (LYs) and QALYs lived in comparison to VKAs.

Table 31 LY and QALY outcomes of apixaban vs VKA

	Expected effects with apixaban	Expected effects with VKA	Incremental effect
LYs (undiscounted)	11.455	10.847	0.608
LYs (discounted)	9.318	8.900	0.418
QALYs (undiscounted)	9.256	8.711	0.545
QALYs (discounted)	7.537	7.157	0.380

Abbreviations:
LY: life year; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist

The incremental cost-effectiveness of apixaban vs VKAs is presented in ***Table 32***. Over a lifetime horizon, apixaban, in comparison to VKAs, resulted in cost savings and greater QALYs lived. Apixaban therefore dominated VKAs.

Table 32 Incremental cost-effectiveness of apixaban vs VKA

	Cost per patient (CHF)	Incremental cost (CHF)	QALYs per patients	Incremental QALYs	ICER (CHF per QALY gained)
Apixaban	25,856.02	–6,295.06	7.537	0.380	Dominant
VKA	32,151.08	NA	7.157	NA	NA

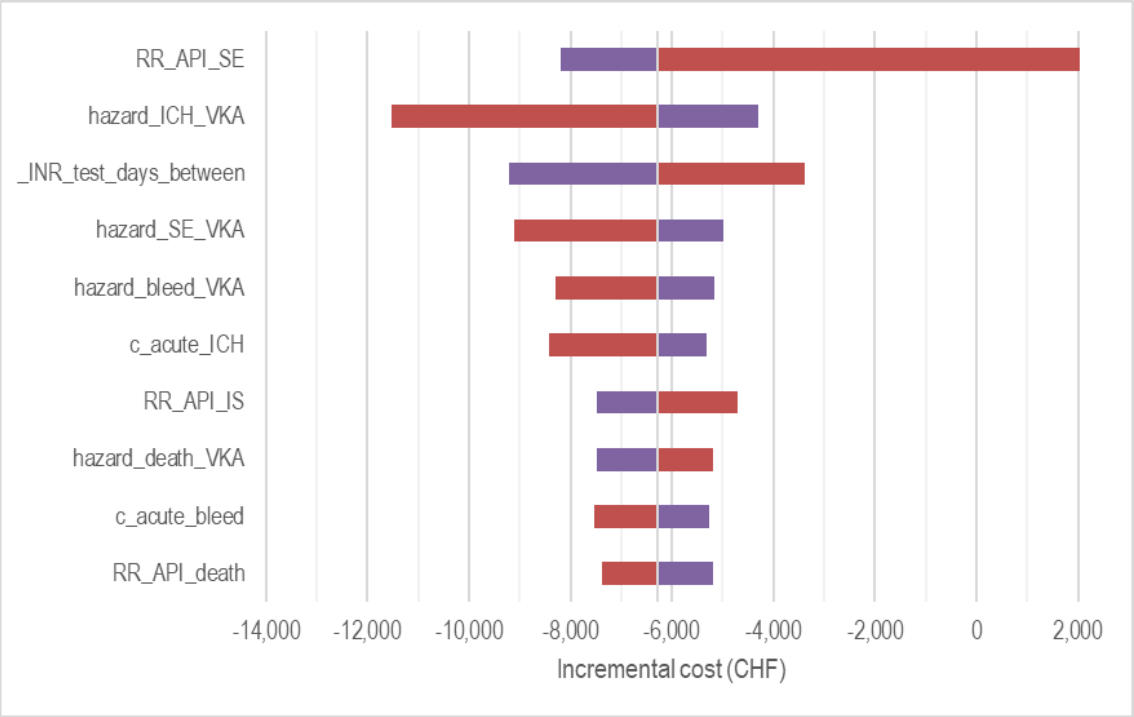
Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **NA**: not applicable; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.

8.2.6.1.2 Univariate sensitivity analysis

Univariate DSAs were used to identify key model drivers of the apixaban vs VKA comparison. The impact of each variable on the incremental cost, incremental QALYs, and the ICER, were explored. The top 10 drivers are presented visually using tornado diagrams (***Figure 37***, ***Figure 38*** and **Figure 39**).

The top drivers of incremental cost were the relative efficacy of apixaban (vs VKA) with respect to SE (due to the large uncertainty range of this parameter), the baseline hazard of ICH and the interval between INR testing for patients receiving VKA (***Figure 37***). The incremental costs increased above zero on one occasion: toward the upper bounds of the relative efficacy of apixaban with respect to SE.

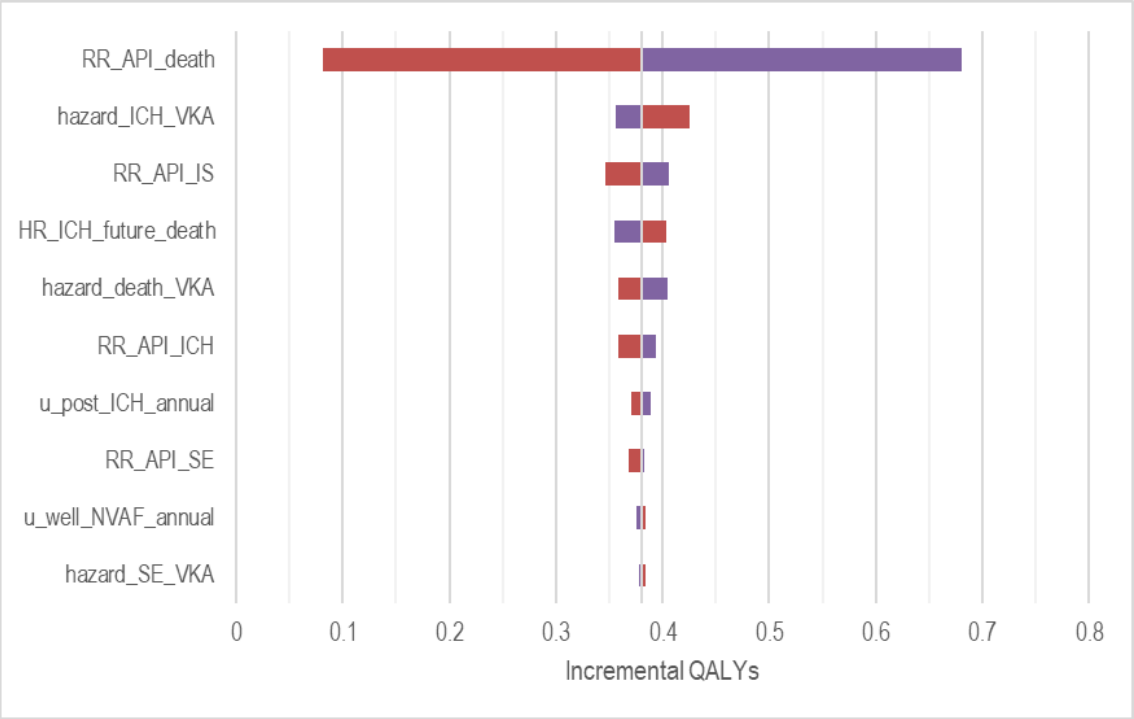
Figure 37 Tornado diagram on the incremental cost of apixaban vs VKA



Abbreviations:
API: apixaban; **CHF**: Swiss francs; **ICH**: intracranial haemorrhage; **INR**: international normalised ratio; **IS**: ischaemic stroke; **RR**: relative risk; **SE**: systemic embolism; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

The major driver of incremental QALYs was the relative efficacy of apixaban (vs VKA) with respect to all-cause mortality (***Figure 38***). Moderate drivers of incremental effectiveness included the baseline hazard of ICH, the relative efficacy of apixaban (vs VKA) with respect to IS, the baseline hazard of all-cause mortality and the impact of a history of ICH on future risk of death (***Figure 38***). The incremental effectiveness remained positive (i.e. in favour of apixaban) across the ranges of all variables (***Figure 38***).

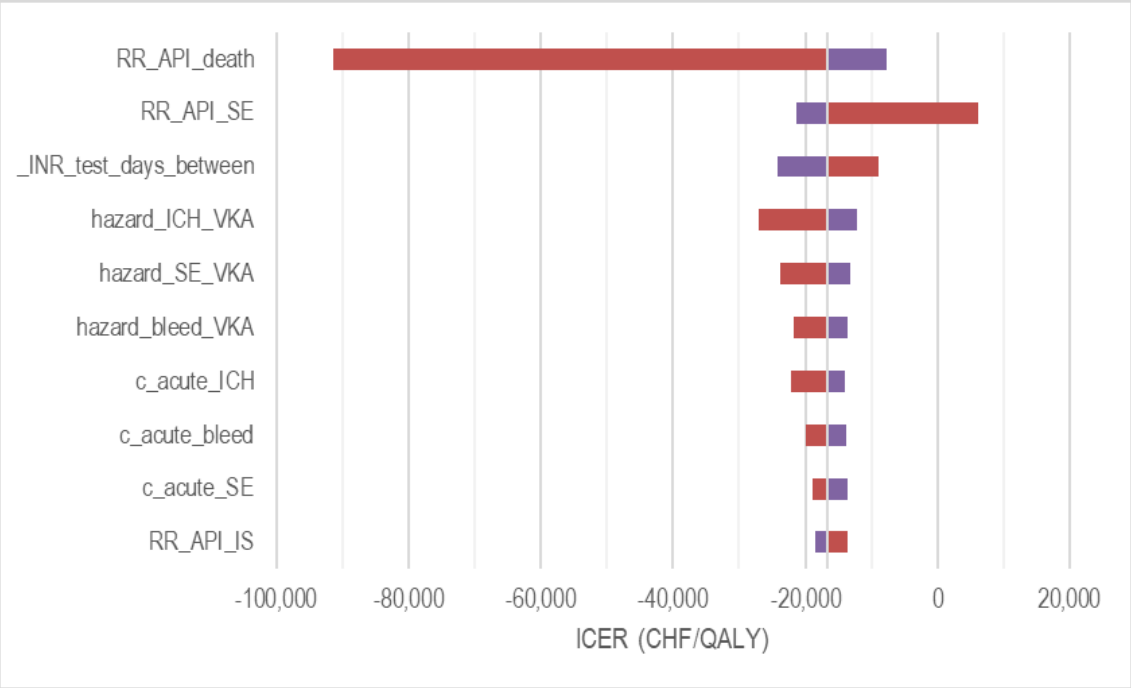
Figure 38 Tornado diagram on the incremental QALYs of apixaban vs VKA



Abbreviations:
API: apixaban; **ICH**: intracranial haemorrhage; **IS**: ischaemic stroke; **NVAF**: nonvalvular atrial fibrillation; **QALY**: quality-adjusted life year; **RR**: relative risk; **SE**: systemic embolism; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

The tornado diagrams above (***Figure 37*** and ***Figure 38***) indicate that the dominance of apixaban over VKAs was robust to uncertainty in almost all input parameters. Overall, the relative efficacy of apixaban (vs VKA) on all-cause mortality was the most important driver of the ICER (***Figure 39***). The interval between INR testing for patients on VKAs and relative efficacy of apixaban on SE were also important drivers (***Figure 39***). The ICER became positive on one occasion: toward the upper bound of the relative efficacy of apixaban with respect to SE. This change reflects a change in incremental cost from negative to positive (as shown in ***Figure 37***). Nevertheless, the resulting ICER remained very small, suggesting the overall conclusion of cost-effectiveness in favour of apixaban is robust.

Figure 39 Tornado diagram on the ICER of apixaban vs VKA

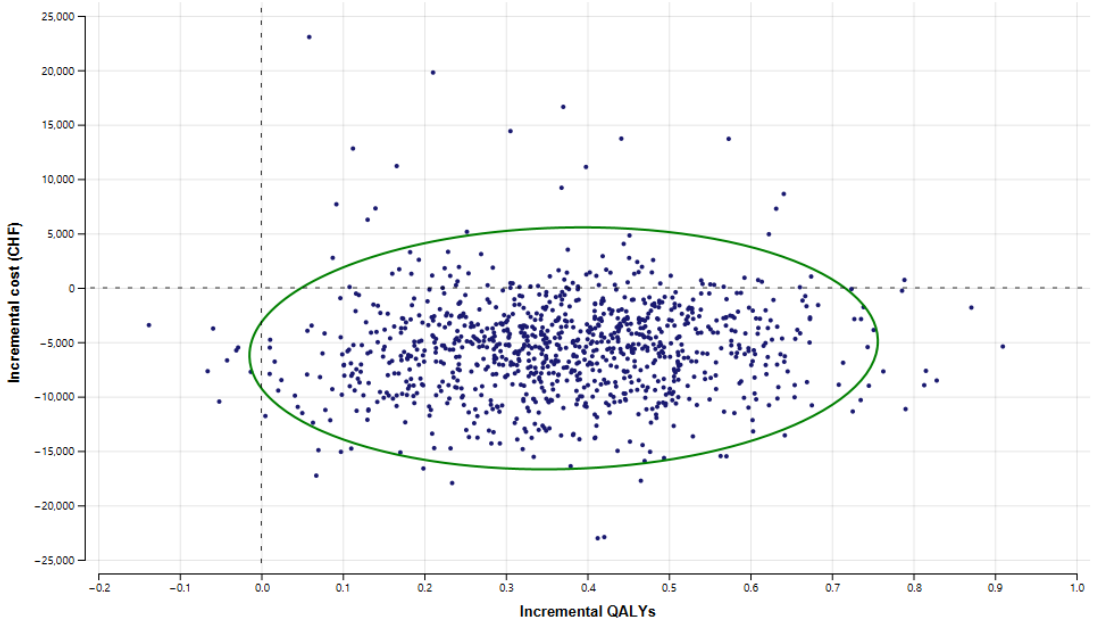


Abbreviations:
API: apixaban; **CHF**: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **ICH**: intracranial haemorrhage; **INR**: international normalised ratio; **QALY**: quality-adjusted life year; **RR**: relative risk; **SE**: systemic embolism; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

8.2.6.1.3 Probabilistic sensitivity analysis

Most iterations of the PSA undertaken for the apixaban vs VKA comparison fell in the south-east quadrant of the CE plane, indicating a high degree of certainty that apixaban is dominant (i.e. less costly and more effective) over VKA (***Figure 40***). Given this finding, a CEAC was not produced.

Figure 40 Incremental cost-effect pairs on the CE plane for apixaban vs VKA



Abbreviations:
CE: cost-effectiveness; CHF: Swiss francs; QALY: quality-adjusted life year; VKA: vitamin K antagonist.

8.2.6.1.4 Scenario analysis

A series of scenario or structural sensitivity analyses was undertaken to explore the impact of certain structural or other assumptions on the cost-effectiveness outcomes. Results of the scenario analysis performed on the apixaban vs VKA comparison are presented in ***Table 33***.

The scenarios having the greatest influence on incremental costs were: removing the additional monitoring costs associated with VKAs, changing the start age, including long-term costs after IS and ICH and assuming patients discontinue OAC after ICH. Reducing the start age, assuming patients discontinue OAC after ICH and included long-term stroke costs favoured apixaban. Increasing the start age favoured VKAs; however, incremental costs remained negative (i.e. apixaban remained cost-saving). Removing the additional monitoring costs associated with VKAs inverted the incremental costs to positive.

Scenarios having the greatest influence on incremental QALYs were: reducing the time horizon, which reduced incremental QALYs, and assuming patients discontinued OAC after ICH, which increased incremental QALYs (i.e. favoured apixaban). Only one scenario inverted the dominance of apixaban; however, the ICER remained low, at CHF3,976.15 per QALY gained.

Table 33 ICER outcomes from the scenario analyses for apixaban vs VKA

Scenario	Incremental costs (CHF)	Incremental QALYs	ICER
Base case	–6,295.06	0.380	Dominant
Time horizon: 5 years	–2,603.92	0.041	Dominant
Time horizon: 10 years	–4,858.98	0.142	Dominant
Discontinue OAC after ICH [a]	–10,545.63	0.608	Dominant
Start age: 60 years	–11,943.68	0.464	Dominant
Start age:80 years	–2,291.94	0.260	Dominant
No long-term disutility after stroke (i.e. IS or ICH)	–6,295.06	0.352	Dominant
Include long-term stroke costs [b]	–10,689.31	0.380	Dominant
Include additional costs for acute stroke events	–9,188.04	0.380	Dominant
No VKA monitoring costs [c]	1,509.45	0.380	CHF3,976.15/QALY gained
No increased mortality risk after ICH	–6,773.88	0.356	Dominant
No increased event risk after any previous IS or ICH	–3,757.88	0.348	Dominant
Discount rate: 0% p.a.	–7,649.88	0.545	Dominant
Discount rate: 6% p.a.	–5,280.85	0.274	Dominant

Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **ICH**: intracranial haemorrhage; **IS**: ischaemic stroke; **OAC**: oral anticoagulation; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.
Notes:
[a] For patients with a history of ICH, hazard ratios reflecting the relative effect of no treatment in comparison to VKAs were applied. These hazard ratios are summarised in ***Table 126, Appendix D***).
[b] An arbitrary value of CHF5,000 per 3-month cycle was assigned to patients with a history of IS, ICH, or IS & ICH.
[c] Monitoring costs for patients on VKA were set equal to those for patients on DOAC (i.e. 2.5 GP visits per year).

8.2.6.1.5 NRSI evidence for relative efficacy estimates

The incremental cost effectiveness of apixaban vs VKAs based on relative efficacy estimates from the NRSIs are presented in ***Table 34***. Over a lifetime horizon, apixaban was associated with cost savings in comparison to VKAs; however, apixaban resulted in less QALYs lived. The ICER was estimated at CHF14,163.81 per QALY gained, indicating that for each QALY gained with VKAs, an additional cost of CHF14,163.81 would be incurred.

Table 34 Incremental cost effectiveness of apixaban based on NRSI relative effects

	Cost per patient (CHF)	Incremental cost (CHF)	QALYs per patient	Incremental QALYs	ICER (CHF per QALY gained)
Apixaban	26,645.99	–5,505.09	6.768	–0.389	NA
VKA	32,151.08	NA	7.157	NA	14,163.81

Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **NA**: not applicable; **NRSI**: non-randomised studies of intervention; **QALY**: quality-adjusted life years; **VKA**: vitamin K antagonists.

As was done for the primary analysis, one-way DSA and PSA were also undertaken on the model, using NRSI-based estimates of relative effect to explore the overall certainty of the economic outcomes reached based on real-world evidence (***Section 17.4.1***, ***Appendix D***).

The most influential driver of both costs and effects was the relative risk of apixaban (vs VKA) on all-cause mortality (***Figure 53*** and ***Figure 54***, ***Appendix D***). At its lower bound (HR: 0.88), apixaban was less costly and more effective than VKAs (i.e. dominant). At its upper bound (HR: 1.54) apixaban was less costly but less effective than VKAs (ICER [VKAs vs apixaban]: CHF7,547.29/QALY).

NRSI-based analysis findings disagreed with results of the RCT-based analysis, which indicated with a high degree of certainty that apixaban was dominant over VKAs. PSA iterations from the NRSI-based analysis fell in all 4 quadrants of the CE plane; the largest portion falling in the south-west quadrant (i.e. apixaban less costly and less effective than VKA) (***Figure 55***, ***Appendix D***). From the CEAC curve, it is apparent that, beyond a WTP threshold of around CHF60,000, VKAs have an approximate 80% probability of being cost-effective over apixaban (***Figure 56***, ***Appendix D***).

8.2.6.2 Dabigatran vs VKA

8.2.6.2.1 ICER

The expected costs (disaggregated) of dabigatran vs VKAs are presented in ***Table 35***. Dabigatran was more expensive in terms of drug costs than VKAs; however, it was cost-saving in terms of monitoring costs and clinical event costs (***Table 35***). Overall, dabigatran was cost-saving in comparison to VKAs.

Table 35 Disaggregated costs of dabigatran vs VKA

Cost Component	Expected costs with dabigatran (CHF)	Expected costs with VKA (CHF)	Incremental cost (CHF)
Drug costs	10,357.27	461.95	9,895.32
Monitoring costs	990.79	8,745.48	–7,754.69
Clinical event costs	17,033.14	22,943.65	–5,910.51
TOTAL	28,381.20	32,151.08	–3,769.88

Abbreviations:
CHF: Swiss francs; **VKA**: vitamin K antagonist.

The expected outcomes of dabigatran vs VKAs are presented in ***Table 37***. Dabigatran was associated with greater LYs and QALYs lived in comparison to VKAs.

Table 36 LY and QALY outcomes of dabigatran vs VKA

	Expected effects with dabigatran	Expected effects with VKA	Incremental effect
LYs (undiscounted)	11.534	10.847	0.687
LYs (discounted)	9.371	8.900	0.471
QALYs (undiscounted)	9.333	8.711	0.622
QALYs (discounted)	7.590	7.157	0.432

Abbreviations:
LY: life year; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.

The incremental cost-effectiveness of dabigatran vs VKAs is presented in ***Table 37***. Over a lifetime horizon, dabigatran resulted in cost savings and greater QALYs lived relative to VKAs. Dabigatran thus dominated VKAs.

Table 37 Incremental cost-effectiveness ratio of dabigatran vs VKA

	Cost per patient (CHF)	Incremental cost (CHF)	QALYs per patient	Incremental QALYs	ICER (CHF per QALY gained)
Dabigatran	28,381.20	–3,769.88	7.590	0.432	Dominant
VKA	32,151.08	NA	7.157	NA	NA

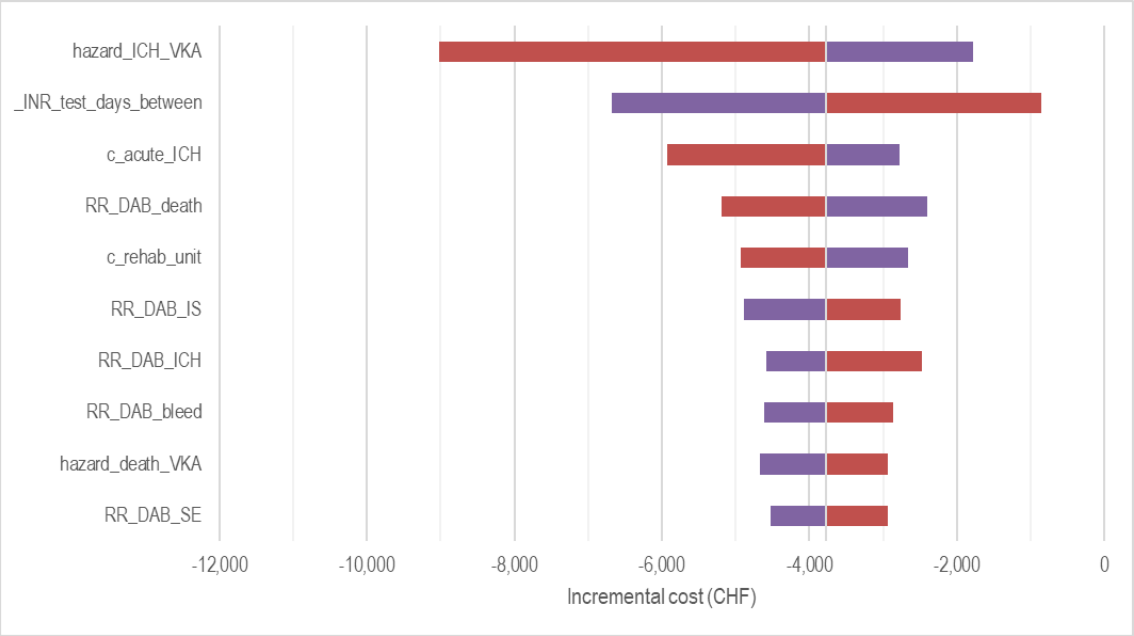
Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.

8.2.6.2.2 Univariate sensitivity analysis

Univariate DSAs were used to identify key model drivers of the dabigatran vs VKA comparison. The impact of each variable on the incremental cost, incremental effects and the ICER were explored. The top 10 drivers are presented visually using tornado diagrams (***Figure 41***, ***Figure 42*** and ***Figure 43***).

The top drivers of the incremental cost were the baseline hazard of ICH and the interval between INR testing for patients receiving VKA (***Figure 41***). The cost to treat ICH, the relative efficacy of dabigatran (vs VKAs) with respect to all-cause mortality and the unit cost for inpatient rehabilitation were also important drivers (***Figure 41***). Neither the upper nor lower bounds of any variables increased the incremental costs above zero (***Figure 41***).

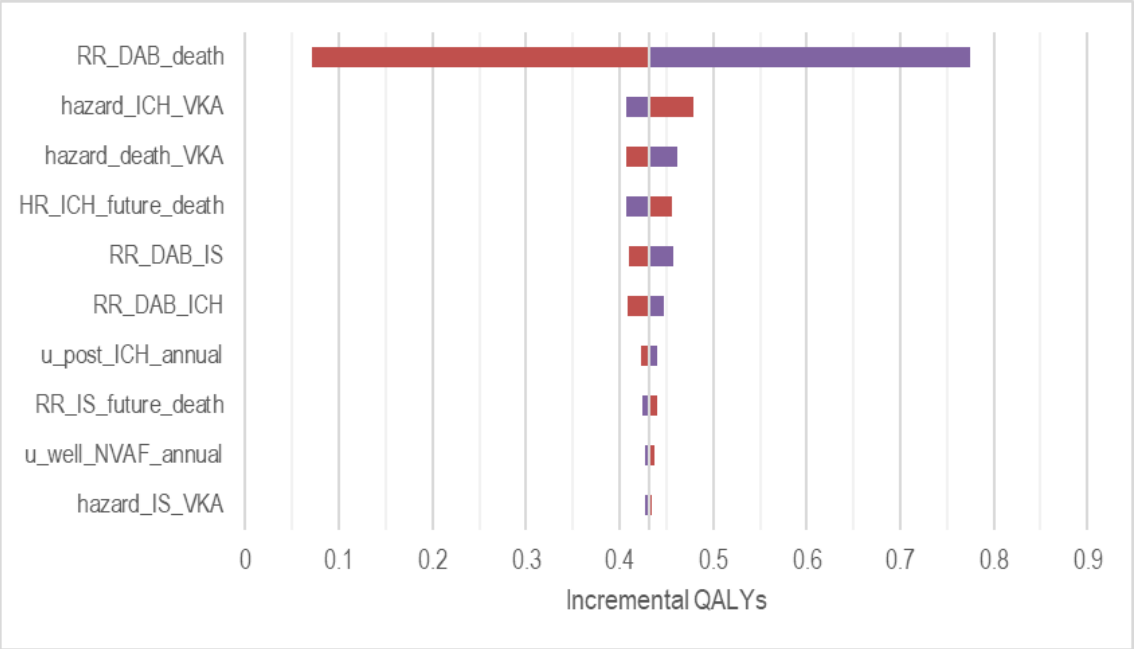
Figure 41 Tornado diagram on the incremental cost of dabigatran vs VKA



Abbreviations:
CHF: Swiss francs; **DAB**: dabigatran; **ICH**: intracranial haemorrhage; **INR**: international normalised ratio; **IS**: ischaemic stroke; **RR**: relative risk; **SE**: systemic embolism; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

The major driver of incremental QALYs was the relative efficacy of dabigatran (vs VKAs) with respect to all-cause mortality (***Figure 42***). Moderate drivers of incremental QALYs included the baseline hazards of ICH and all-cause mortality, the relative efficacy of dabigatran (vs VKAs) with respect to IS and ICH, and the impact of a history of ICH on future risk of death (***Figure 42***). The incremental effectiveness remained positive (i.e. in favour of dabigatran) across the upper and lower bounds of all variables (***Figure 42***).

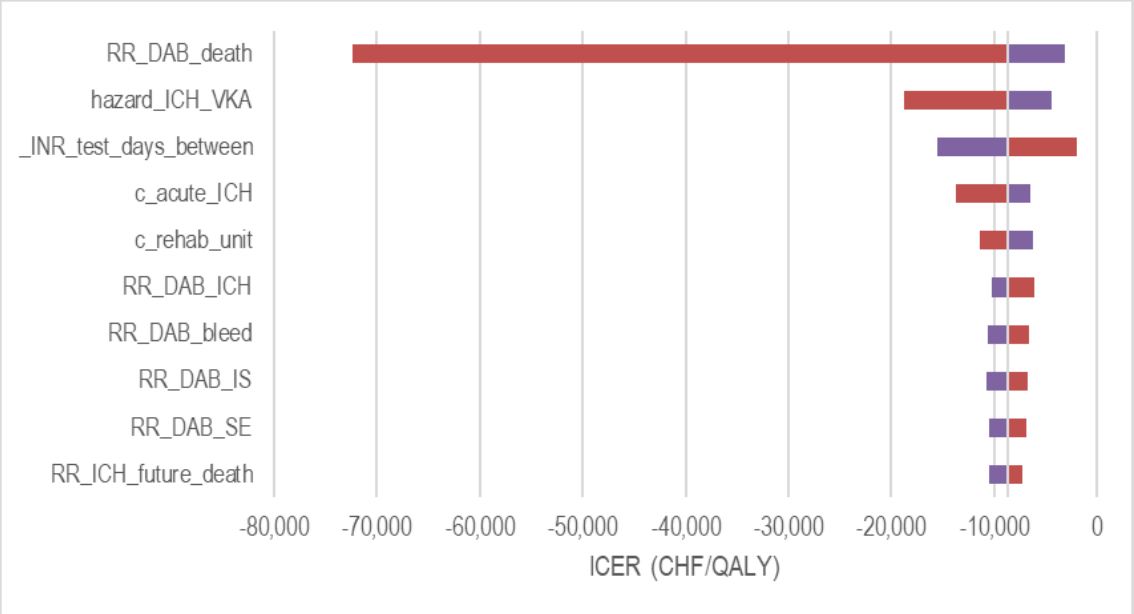
Figure 42 Tornado diagram on the incremental QALYs of dabigatran vs VKA



Abbreviations:
DAB: dabigatran; **ICH**: intracranial haemorrhage; **IS**: ischaemic stroke; **NVAF**: nonvalvular atrial fibrillation; **QALY**: quality-adjusted life year; **RR**: relative risk; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

The tornado diagrams above (***Figure 41*** and ***Figure 42***) indicate that the dominance of dabigatran over VKAs was robust to uncertainty in all input parameters. Overall, the relative efficacy of dabigatran (vs VKA) with respect to all-cause mortality was the most important driver of the ICER (***Figure 43***). The interval between INR testing for patients on VKAs and the baseline hazard of ICH were also important drivers.

Figure 43 Tornado diagram on the ICER of dabigatran vs VKA

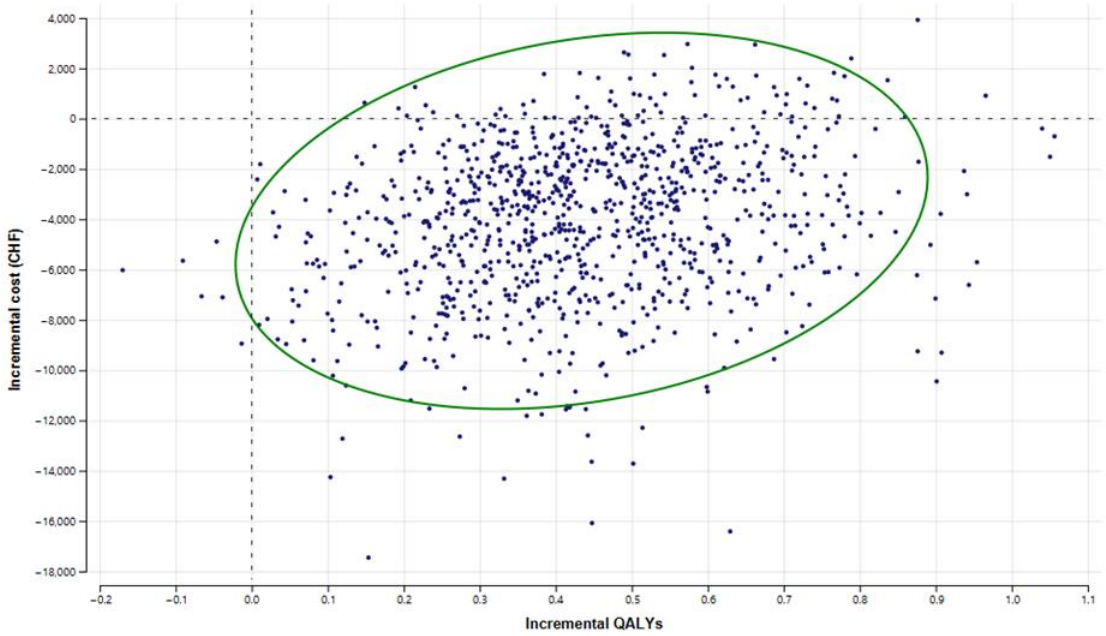


Abbreviations:
CHF: Swiss francs; **DAB**: dabigatran; **ICER**: incremental cost-effectiveness ratio; **ICH**: intracranial haemorrhage; **INR**: international normalised ratio; **IS**: ischaemic stroke; **QALY**: quality-adjusted life year; **RR**: relative risk; **SE**: systemic embolism; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

8.2.6.2.3 Probabilistic sensitivity analysis

Most iterations of the PSA fell in the south-east quadrant of the CE plane, indicating a high degree of certainty that dabigatran is dominant (i.e. less costly and more effective) over VKAs (***Figure 44***). Given this finding, a CEAC was not produced.

Figure 44 Incremental cost-effect pairs on the CE plane for dabigatran vs VKA



Abbreviations:
CE: cost-effectiveness; **CHF**: Swiss francs; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.

8.2.6.2.4 Scenario analysis

A series of scenario or structural sensitivity analyses was undertaken to explore the impact of certain structural assumptions or other factors on the cost-effectiveness outcomes. Results of the scenario analysis performed on the dabigatran vs VKA comparison are presented in ***Table 38***.

The scenarios having the greatest influence on incremental costs were: removing the additional monitoring costs associated with VKAs, including long-term costs after IS and ICH, reducing the start age to 60 years, assuming patients discontinue OAC after ICH and including additional event costs for IS and ICH (***Table 38***). Assuming patients discontinue OAC after ICH, reducing the start age to 60 years, including long-term costs after IS and ICH and including additional event costs for IS and ICH all

favoured dabigatran. Removing the additional monitoring costs associated with VKAs inverted the incremental costs to positive, favouring VKAs.

Scenarios having the greatest influence on incremental QALYs were: reducing the time horizon, which reduced incremental QALYs, and assuming patients discontinued OAC after ICH, which increased incremental QALYs (i.e. favoured dabigatran) (***Table 38***).

Only one scenario inverted the dominance of dabigatran; however, the ICER remained low, at CHF9,337.73 per QALY gained (***Table 38***).

Table 38 ICER outcomes from the scenario analyses for dabigatran vs VKA

Scenario	Incremental costs (CHF)	Incremental QALYs	ICER
Base case	–3,769.88	0.432	Dominant
Time horizon: 5 years	–1,516.82	0.045	Dominant
Time horizon: 10 years	–3,005.12	0.160	Dominant
Discontinue OAC after ICH [a]	–7,732.66	0.683	Dominant
Reduced dose (110 mg twice daily)	–3,065.96	0.298	Dominant
Start age: 60 years	–8,339.68	0.533	Dominant
Start age: 80 years	–944.77	0.292	Dominant
No long-term disutility after stroke (i.e. IS or ICH)	–3,769.88	0.396	Dominant
Include long-term stroke costs [b]	–9,899.09	0.432	Dominant
Include additional costs for acute stroke events	–7,402.27	0.432	Dominant
No VKA monitoring costs [c]	4,034.63	0.432	CHF9,337.73/QALY gained
No increased mortality risk after ICH	–4,236.83	0.408	Dominant
No increased event risk after any previous IS or ICH	–1,201.66	0.390	Dominant
Discount rate: 0%	–4,521.32	0.621	Dominant
Discount rate: 6%	–3,184.16	0.311	Dominant

Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **ICH**: intracranial haemorrhage; **IS**: ischaemic stroke; **OAC**: oral anticoagulation; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.
Notes:
[a] For patients with a history of ICH, hazard ratios reflecting the relative effect of no treatment in comparison to VKAs were applied. These hazard ratios are summarised in ***Table 126***, ***Appendix D***).
[b] An arbitrary value of CHF5,000 per 3-month cycle was assigned to patients with a history of IS, ICH, or IS & ICH.
[c] Monitoring costs for patients on VKA were set equal to those for patients on DOAC (i.e. 2.5 GP visits per year).

8.2.6.2.5 NRSI evidence for relative efficacy estimates

The incremental cost effectiveness of dabigatran vs VKAs, based on relative efficacy estimates from the NRSI meta-analysis are presented in ***Table 39***. Over a lifetime horizon, dabigatran was associated with cost savings as well as increased QALYs lived in comparison to VKAs. Dabigatran thus dominated VKAs.

Table 39 Incremental cost effectiveness of dabigatran based on NRSI relative effects

	Cost per patient (CHF)	Incremental cost (CHF)	QALYs per patient	Incremental QALYs	ICER (CHF per QALY gained)
Dabigatran	28,993.49	–3,157.58	7.193	0.036	Dominant
VKA	32,151.08	NA	7.157	NA	NA

Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **NA**: not applicable; **NRSI**: non-randomised studies of intervention; **QALY**: quality-adjusted life years; **VKA**: vitamin K antagonists.

As done for the primary analysis, one-way DSA and PSA were also undertaken on the model using NRSI relative efficacy estimates to explore the overall certainty of the economic outcomes reached based on real-world evidence (***Section 17.4.2***, ***Appendix D***).

Incremental cost changed from negative to positive (i.e. in favour of VKA) on one occasion: toward the upper bound of the relative effect of dabigatran with respect to IS (***Figure 57, Appendix D***). The relative effect of dabigatran (vs VKAs) with respect to IS was the second most influential driver of the incremental costs and the second most important driver of incremental QALYs (***Figure 57*** and ***Figure 58, Appendix D***). At its lower bound (HR: 0.80), dabigatran was dominant over VKAs while at its upper bound (HR: 1.64) dabigatran was dominated. The baseline hazard of ICH was the most influential driver of incremental costs and the third most important driver of incremental QALYs; however, dabigatran remained dominant across the full uncertainty range of this variable.

Two variables inverted the incremental QALYs from positive to negative (i.e. in favour of VKA): the relative efficacies of dabigatran with respect to all-cause mortality and IS (***Figure 58***, ***Appendix D***). The relative effect of dabigatran with respect to all-cause mortality was the most influential driver of incremental QALYs (***Figure 58***, ***Appendix D***). At its lower bound (HR: 0.92), dabigatran was dominant over VKAs while at its upper bound (HR: 1.09), dabigatran was less costly but less effective than VKAs (ICER [VKAs vs dabigatran]: CHF20,582.69/QALY).

In comparison to the RCT-based analysis, which indicated with a high degree of certainty that dabigatran was dominant over VKAs, the NRSI-based analysis was less clear. PSA iterations were distributed across all 4 quadrants of the CE plane (***Figure 59, Appendix D***). Iterations were relatively well distributed across the eastern and western quadrants indicating uncertainty as to whether dabigatran or VKAs are associated with greater QALYs gained. Most iterations lay in the southern as opposed to northern quadrant, indicating a higher probability that dabigatran is cost-saving as opposed to more costly than VKA. From the CEAC curve, it is apparent that dabigatran has a higher probability of being cost-effective, but this probability drops below 70% beyond a WTP of approximately CHF100,000 per QALY(***Figure 60, Appendix D***).

8.2.6.3 Edoxaban vs VKA

8.2.6.3.1 ICER

The expected costs (disaggregated) of edoxaban vs VKAs are presented in ***Table 40***. Edoxaban was more expensive in terms of drug costs than VKAs; however, it was cost-saving in terms of monitoring costs and clinical event costs (***Table 40***). Overall, edoxaban was cost-saving in comparison to VKAs.

Table 40 Disaggregated costs of edoxaban vs VKA

Cost Component	Expected costs with edoxaban (CHF)	Expected costs with VKA (CHF)	Incremental cost (CHF)
Drug costs	9,271.18	461.95	8,809.23
Monitoring costs	975.90	8,745.48	–7,769.58
Clinical event costs	17,384.38	22,943.65	–5,559.27
TOTAL	27,631.46	32,151.08	–4,519.61

Abbreviations:
CHF: Swiss francs; **VKA**: vitamin K antagonist.

The expected outcomes of edoxaban vs VKAs are presented in ***Table 41***. Edoxaban was associated with greater LYs and QALYs lived in comparison to VKAs.

Table 41 LY and QALY outcomes of edoxaban vs VKA

	Expected effects with edoxaban	Expected effects with VKA	Incremental effect
LYs (undiscounted)	11.326	10.847	0.479
LYs (discounted)	9.231	8.900	0.331
QALYs (undiscounted)	9.139	8.711	0.428
QALYS (discounted)	7.456	7.157	0.298

Abbreviations:
LY: life year; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.

The incremental cost-effectiveness of edoxaban vs VKAs is presented in ***Table 42.*** Over a lifetime horizon, edoxaban resulted in cost savings and greater QALYs lived than VKAs, thus being dominant over VKAs.

Table 42 Incremental cost-effectiveness ratio of edoxaban vs VKA

	Cost per patient (CHF)	Incremental cost (CHF)	QALYs per patient	Incremental QALYs	ICER (CHF per QALY gained)
Edoxaban	27,631.46	–6,423.79	7.456	0.298	Dominant
VKA	32,151.08	NA	7.157	NA	NA

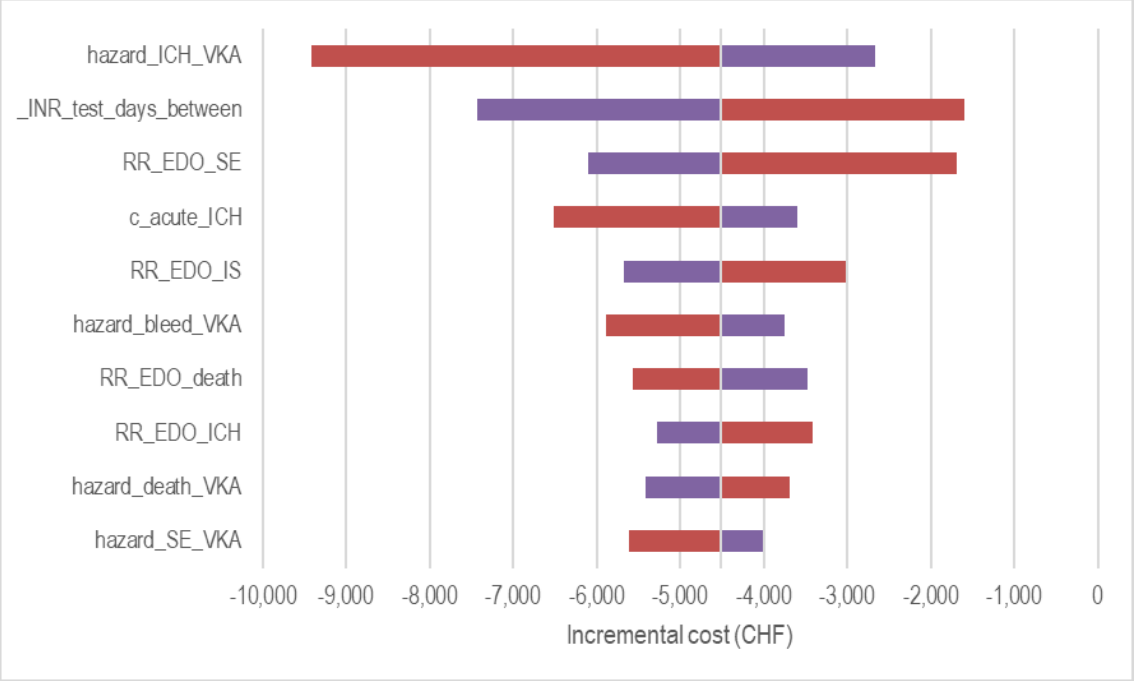
Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.

8.2.6.3.2 Univariate sensitivity analysis

Univariate DSAs were used to identify key model drivers of the edoxaban vs VKAs comparison. The impact of each variable on the incremental costs and incremental effects, as well as on the ICER, were explored. The top 10 drivers are presented visually using tornado diagrams (***Figure 45***, ***Figure 46*** and ***Figure 47***).

The top drivers of the incremental cost were: the baseline annual hazard of ICH and the interval between INR testing for patients receiving a VKA (***Figure 45***). The relative efficacy of edoxaban (vs VKAs) with respect to SE and IS, and acute treatment costs of ICH were also important drivers of the incremental cost (***Figure 45***). Neither the upper nor lower bounds of any variables increased the incremental costs above zero (***Figure 45***).

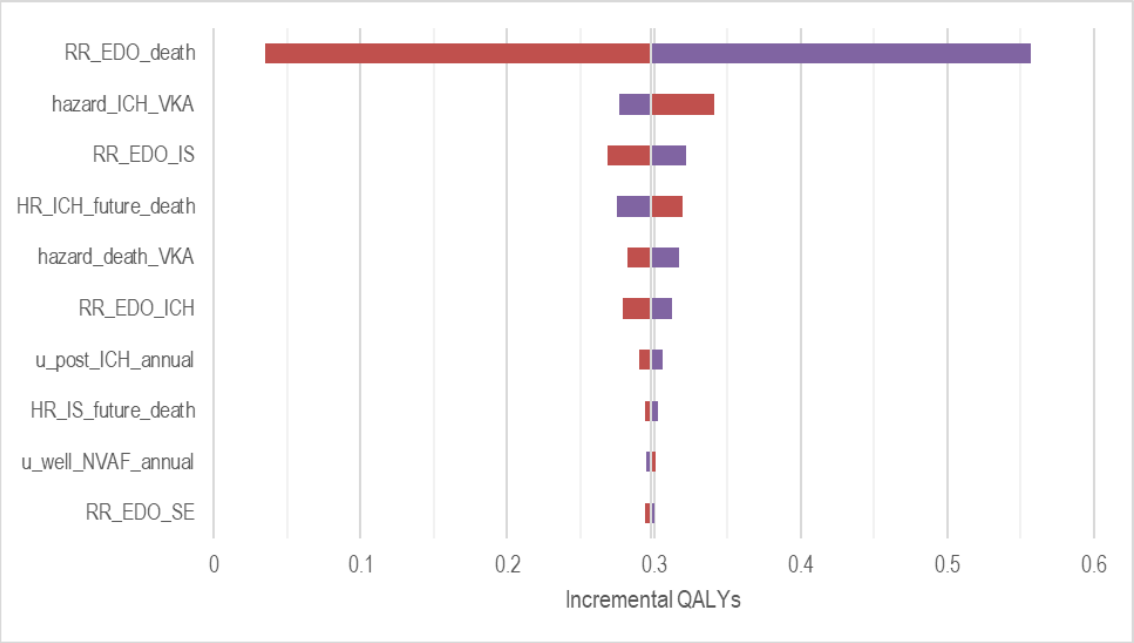
Figure 45 Tornado diagram on the incremental cost of edoxaban vs VKA



Abbreviations:
CHF: Swiss francs; **EDO**: edoxaban; **ICH**: intracranial haemorrhage; **INR**: international normalised ratio; **IS**: ischaemic stroke; **RR**: relative risk; **SE**: systemic embolism; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

The major driver of the incremental effectiveness was the relative efficacy of edoxaban (vs VKAs) with respect to all-cause mortality (***Figure 46***). Moderate drivers of incremental effectiveness included the baseline annual hazard of ICH, the relative efficacy of dabigatran (vs VKAs) with respect to IS, the baseline hazard of all-cause mortality, and the impact of a history of ICH on future risk of death (***Figure 46***). The incremental effectiveness remained positive (i.e. in favour of edoxaban) across the upper and lower bounds of all variables (***Figure 46***).

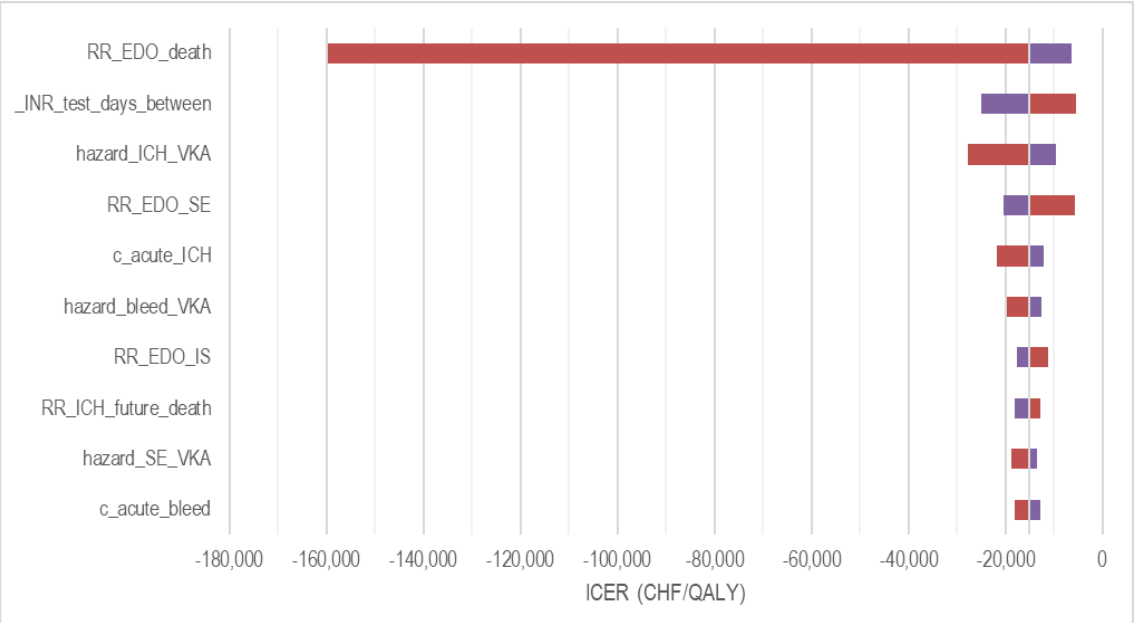
Figure 46 Tornado diagram on the incremental QALYs of edoxaban vs VKA



Abbreviations:
EDO: edoxaban; **HR**: hazard ratio; **ICH**: intracranial haemorrhage; **IS**: ischaemic stroke; **NVAF**: nonvalvular atrial fibrillation; **QALY**: quality-adjusted life year; **RR**: relative risk; **SE**: systemic embolism; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

The tornado diagrams above (***Figure 45*** and ***Figure 46***) demonstrate that the conclusion of dominance (i.e. that edoxaban is less costly and more effective than VKAs) was robust to uncertainty in all input parameters. Overall, the relative efficacy of edoxaban (vs VKA) with respect to all-cause mortality was the most important driver of the ICER (***Figure 47***). The interval between INR testing for patients on VKAs and the baseline hazard of ICH were also important drivers (***Figure 47***).

Figure 47 Tornado diagram on the ICER of edoxaban vs VKA

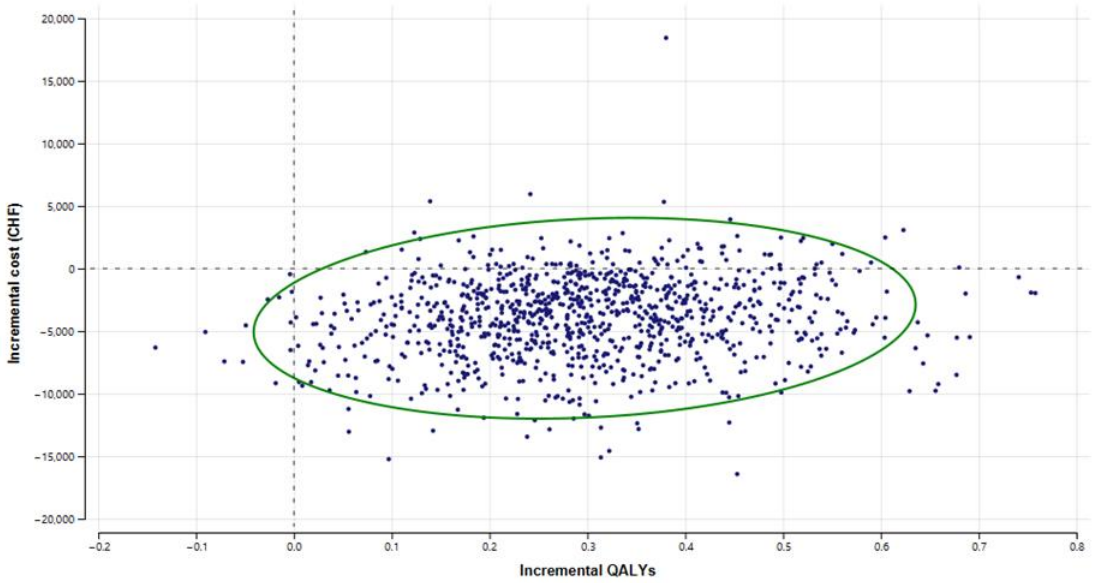


Abbreviations:
CHF: Swiss francs; **EDO**: edoxaban; **HR**: hazard ratio; **ICH**: intracranial haemorrhage; **INR**: international normalised ratio; **IS**: ischaemic stroke; **QALY**: quality-adjusted life year; **RR**: relative risk; **SE**: systemic embolism; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

8.2.6.3.3 Probabilistic sensitivity analysis

As shown in ***Figure 48***, most iterations fell in the south-east quadrant of the CE plane, indicating a high degree of certainty that edoxaban is dominant (i.e. less costly and more effective) over VKAs. Given this finding, a CEAC was not produced.

Figure 48 Incremental cost-effect pairs on the CE plane for edoxaban vs VKA



Abbreviations:
CE: cost-effectiveness; **CHF**: Swiss francs; **VKA**: vitamin K antagonist.

8.2.6.3.4 Scenario analysis

A series of scenario or structural sensitivity analyses was undertaken to explore the impact of certain structural assumptions or other factors on the cost-effectiveness outcomes. Results of the scenario analysis performed on the edoxaban vs VKA comparison are presented in ***Table 43***.

The scenarios having the greatest influence on incremental costs were: removing the additional monitoring costs associated with VKAs, changing the start age, assuming patients discontinue OAC after ICH, and including long-term costs after IS and ICH (***Table 43***). Reducing the start age to 60 years, assuming patients discontinue OAC after ICH and adding long-term stroke costs favoured edoxaban. Increasing the start age to 80 years favoured VKAs; however, incremental costs remained negative (i.e. edoxaban remained cost-saving). Removing the additional monitoring costs associated with VKAs inverted the incremental costs to positive.

Scenarios having the greatest influence on incremental QALYs were: reducing the time horizon, which reduced incremental QALYs, and assuming patients discontinued OAC after ICH, which increased incremental QALYs (i.e. favoured edoxaban) (***Table 43***).

Only one scenario inverted the dominance of edoxaban; however, the ICER remained low, at CHF11,015.97 per QALY gained (***Table 43***).

Table 43 ICER outcomes from the scenario analyses for edoxaban vs VKA

Scenario	Incremental costs (CHF)	Incremental QALYs	ICER
Base case	–4,519.61	0.298	Dominant
Tim horizon: 5 years	–1,849.04	0.032	Dominant
Time horizon: 10 years	–3,502.50	0.112	Dominant
Discontinue OAC after ICH [a]	–8,222.88	0.488	Dominant
Start age: 60 years	–8,858.24	0.366	Dominant
Start age: 80 years	–1,548.96	0.203	Dominant
No long-term disutility after stroke (i.e. IS or ICH)	–4,519.61	0.276	Dominant
Include long-term stroke costs [b]	–7,895.55	0.298	Dominant
Include additional costs for acute stroke events	–6,901.59	0.298	Dominant
No VKA monitoring costs [c]	3,284.89	0.298	CHF11,015.97/QALY gained
No increased mortality risk after ICH	–4,956.24	0.276	Dominant
No increased event risk after any previous IS or ICH	–2,473.00	0.273	Dominant
Discount rate: 0%	–5,485.70	0.428	Dominant
Discount rate: 6%	–3,792.38	0.215	Dominant

Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **ICH**: intracranial haemorrhage; **IS**: ischaemic stroke; **OAC**: oral anticoagulation; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.
Notes:
[a] For patients with a history of ICH, hazard ratios reflecting the relative effect of no treatment in comparison to VKAs were applied. These hazard ratios are summarised in ***Table 126, Appendix D***).
[b] An arbitrary value of CHF5,000 per 3-month cycle was assigned to patients with a history of IS, ICH, or IS & ICH.
[c] Monitoring costs for patients on VKA were set equal to those for patients on DOAC (i.e. 2.5 GP visits per year).

8.2.6.3.5 NRSI evidence for relative efficacy estimates

No analysis based on NRSI-based relative efficacy estimates was undertaken for edoxaban given a limited NRSI evidence base.

8.2.6.4 Rivaroxaban vs VKA

8.2.6.4.1 ICER

The expected costs (disaggregated) of rivaroxaban vs VKAs are presented in ***Table 44***. Rivaroxaban was more expensive in terms of drug costs than VKAs; however, it was cost-saving in terms of monitoring costs and clinical event costs (***Table 44***). Overall, rivaroxaban was cost-saving in comparison to VKAs.

Table 44 Disaggregated costs of rivaroxaban vs VKA

Cost Component	Expected costs with rivaroxaban (CHF)	Expected costs with VKA (CHF)	Incremental cost (CHF)
Drug costs	9,760.64	461.95	9,298.69
Monitoring costs	975.00	8,745.48	–7,770.48
Clinical event costs	20,205.50	22,943.65	–2,923.92
TOTAL	30,941.14	32,151.08	–1,209.94

Abbreviations:
CHF: Swiss francs; **VKA**: vitamin K antagonist.

The expected outcomes of rivaroxaban vs VKAs are presented in ***Table 45***. Rivaroxaban was associated with greater LYs and QALYs lived in comparison to VKAs.

Table 45 LY and QALY outcomes of rivaroxaban vs VKA

	Expected effects with rivaroxaban	Expected effects with VKA	Incremental effect
LYs (undiscounted)	11.313	10.847	0.466
LYs (discounted)	9.222	8.900	0.322
QALYs (undiscounted)	9.118	8.711	0.406
QALYs (discounted)	7.441	7.157	0.283

Abbreviations:
LY: life year; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.

The incremental cost-effectiveness of rivaroxaban vs VKAs is presented in ***Table 46***. Over a lifetime horizon, rivaroxaban resulted in cost savings and greater QALYs lived than VKAs, thus being dominant over VKAs.

Table 46 Incremental cost-effectiveness ratio of rivaroxaban vs VKA

	Cost per patient (CHF)	Incremental cost (CHF)	QALYs per patient	Incremental QALYs	ICER (CHF per QALY gained)
Rivaroxaban	30,941.14	–1,209.94	7.441	0.283	Dominant
VKA	32,151.08	NA	7.157	NA	NA

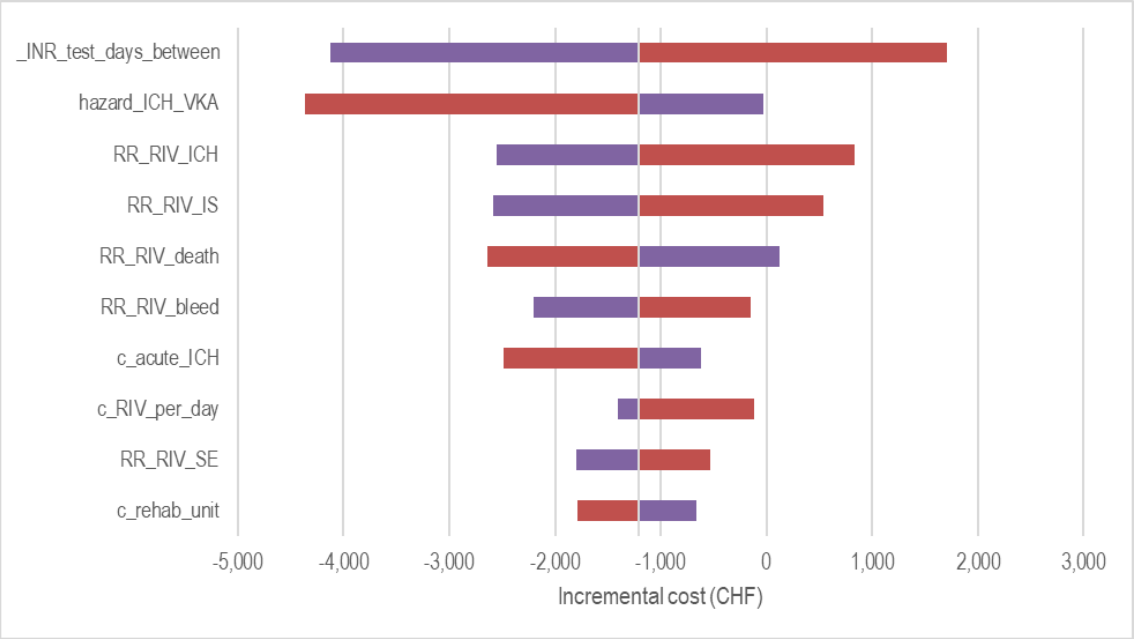
Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.

8.2.6.4.2 Univariate sensitivity analysis

Univariate DSAs were used to identify key model drivers of the rivaroxaban vs VKAs comparison. The impact of each variable on the incremental costs and incremental effects, as well as on the ICER, were explored. Results (incremental costs and effects only) are presented visually using tornado diagrams (***Figure 49*** and ***Figure 50***).

The top drivers of the incremental cost were: the interval between INR testing for patients receiving VKA, the baseline annual hazard of ICH, and the relative efficacies of rivaroxaban with respect to ICH, IS and death (***Figure 49***). The incremental costs increased above zero on 4 occasions: toward the upper bounds of the interval between INR testing for patients receiving VKA and the relative efficacies of rivaroxaban with respect to ICH and ISH, and toward the lower bounds of the relative efficacy of rivaroxaban with respect to all-cause mortality.

Figure 49 Tornado diagram on the incremental cost of rivaroxaban vs VKA

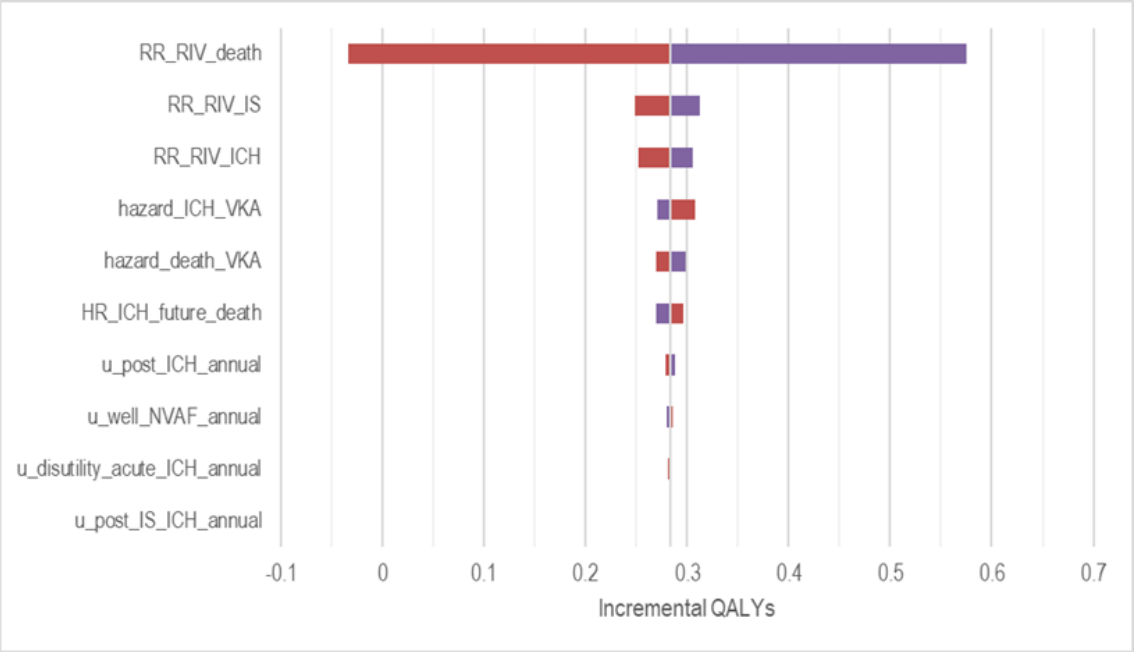


Abbreviations:
CHF: Swiss francs; **ICH**: intracranial haemorrhage; **INR**: international normalised ratio; **IS**: ischaemic stroke; **RIV**: rivaroxaban; **RR**: relative risk; **SE**: systemic embolism; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

The major driver of the incremental effectiveness was the relative efficacy of rivaroxaban (vs VKAs) with respect to all-cause mortality (***Figure 50***). This variable pushed the incremental costs below zero (i.e. favouring VKA) toward its upper bound.

Moderate drivers of incremental effectiveness included the relative efficacy of rivaroxaban (vs VKAs) with respect to IS and ICH (***Figure 50***). The incremental effectiveness remained positive (i.e. in favour of rivaroxaban) across the upper and lower bounds of all remaining variables (***Figure 50***).

Figure 50 Tornado diagram on the incremental QALYs of rivaroxaban vs VKA



Abbreviations:
HR: hazard ratio; **ICH**: intracranial haemorrhage; **IS**: ischaemic stroke; **QALY**: quality-adjusted life year **RIV**: rivaroxaban; **RR**: relative risk; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

The tornado diagrams above (***Figure 49*** and ***Figure 50***) demonstrate that the conclusion of dominance (i.e. that rivaroxaban is less costly and more effective than VKAs) was robust to uncertainty in the majority of input parameters. The ICER value became positive on 4 occasions.

Results with respect to the ICER for the top 5 drivers have been tabulated (***Table 47***). The variability in the ICERs at the upper bounds of these variables across the quadrants of the CE plane precluded the presentation of ICER results using a tornado diagram.

Table 47 Top 5 drivers of the ICER for rivaroxaban vs VKA

Parameter	Lower or upper bound	Incremental cost (CHF)	Incremental QALYs	ICER (CHF/QALY)
RR_RIV_death	0.83 1.03	119.63 –2,643.97	0.575 –0.034	208.20 ICER for VKA vs. RIV: 77,378.88
_INR_test_days_between	15 days 30 days	–4,125.09 1,705.22	0.283 0.283	RIV dominant 6,021.77
hazard_ICH_VKA	0.0057 0.017	–28.87 –4,368.61	0.270 0.308	RIV dominant RIV dominant
RR_RIV_ICH	0.47 0.92	–2,551.43 828.54	0.306 0.253	RIV dominant 3,279.74
RR_RIV_IS	0.74 1.16	–2,590.58 538.19	0.312 0.249	RIV dominant 2,165.65

Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **ICH**: intracranial haemorrhage; **INR**: international normalised ratio; **IS**: ischaemic stroke; **QALY**: quality-adjusted life year; **RIV**: rivaroxaban; **RR**: relative risk; **VKA**: vitamin K antagonist.

Toward the upper bound of the relative efficacy of rivaroxaban with respect to all-cause mortality, rivaroxaban remained less costly but became less effective than VKA; thus, the incremental cost-effect pair lies in the south-west quadrant of the CE plane. At the upper bound of this variable, the cost-effectiveness of rivaroxaban became uncertain. Toward the lower bound of the variable, rivaroxaban remained more effective than VKA but became more costly, moving the cost-effect pair into the north-east quadrant. However, the ICER remained low, at CHF208.20/QALY.

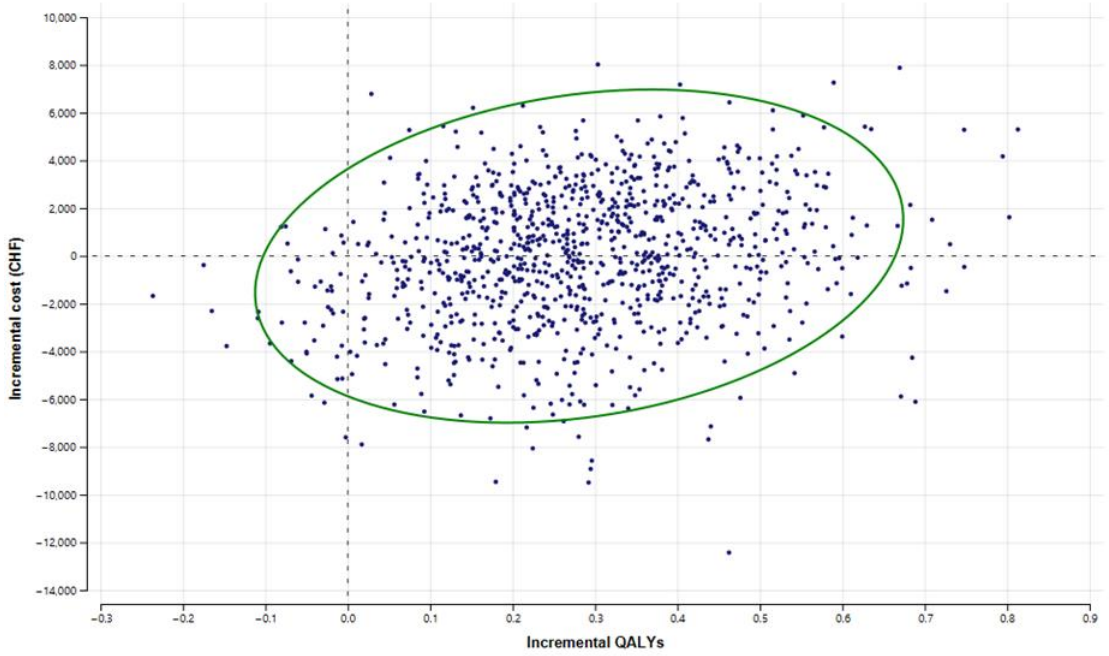
Toward the upper bound of the interval between INR testing for patients on VKA and the relative efficacies of rivaroxaban with respect to ICH and IS, rivaroxaban remained more effective but became more expensive than VKA, with incremental cost-effect pairs falling in the north-east quadrant of the CE plane. Nevertheless, the ICERs remained low, at between CHF2,165.65 and CHF6,021.77 per QALY gained.

8.2.6.4.3 Probabilistic sensitivity analysis

As shown in ***Figure 51***, most iterations were spread across the eastern quadrants (i.e. north-east and south-east quadrants) of the CE plane, indicating a high degree of certainty that rivaroxaban results in greater QALYs gained than VKAs, but suggesting there is uncertainty as to whether costs associated with rivaroxaban are greater than or less than costs associated with VKAs.

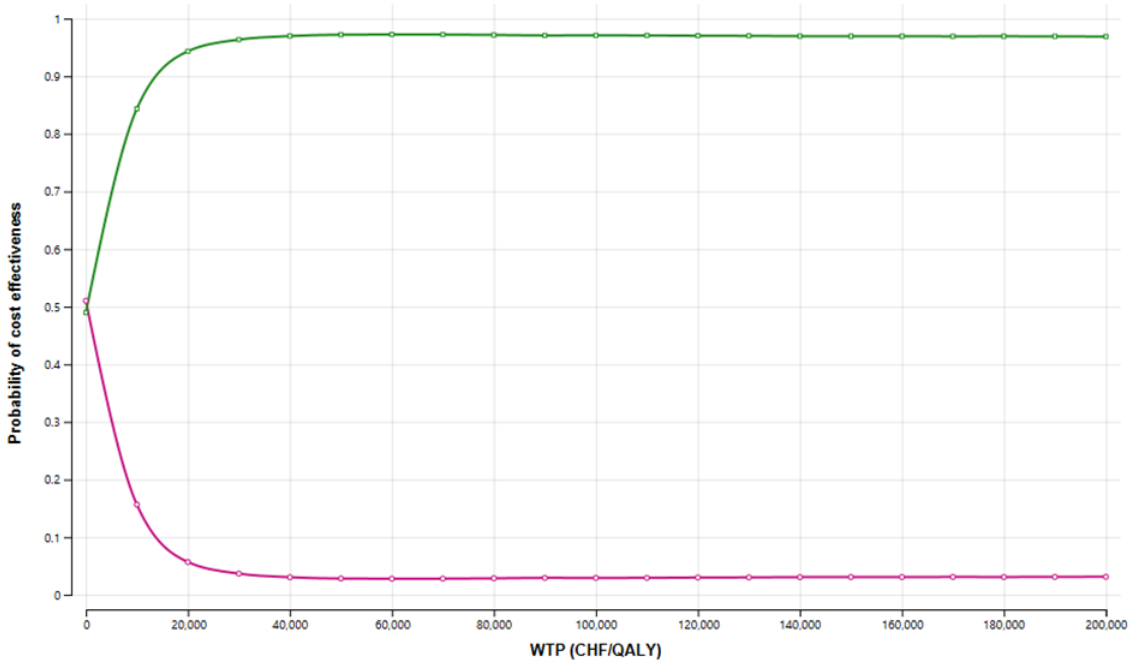
Nevertheless, ***Figure 52*** shows that rivaroxaban is always associated with a greater probability of being cost effective, regardless of the WTP. The probability of cost-effectiveness increases to almost 100% at and above a WTP threshold of CHF40,000 per QALY gained (***Figure 52***).

Figure 51 Incremental cost-effect pairs on the CE plan for rivaroxaban vs VKA



Abbreviations:
CE: cost-effectiveness; **CHF**: Swiss francs; **VKA**: vitamin K antagonist.

Figure 52 CEAC for rivaroxaban vs VKA



Abbreviations:
CEAC: cost-effectiveness acceptability curve; **CHF**: Swiss francs; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist; **WTP**: willingness-to-pay.
Notes:
The green and pink lines represent the probability of cost effectiveness for rivaroxaban and VKA, respectively.

8.2.6.4.4 Scenario analysis

A series of scenario or structural sensitivity analyses was undertaken to explore the impact of certain structural or other assumptions on the cost-effectiveness outcomes. Results are presented in ***Table 48***.

The scenarios having the greatest influence on incremental costs for rivaroxaban vs VKA were: removing the additional monitoring costs associated with VKAs, changing the start age, including long-term costs after IS and ICH, and assuming patients discontinue OAC after ICH (***Table 48***). Reducing the start age to 60 years, including long-term costs after IS and ICH, and assuming patients discontinue OAC after ICH favoured rivaroxaban. Increasing the start age to 80 years favoured VKAs; however, incremental costs remained negative (i.e. rivaroxaban remained cost-saving). Removing the additional monitoring costs associated with VKAs inverted the incremental costs to positive.

Scenarios having the greatest influence on incremental QALYs for rivaroxaban vs VKA were: reducing the time horizon, and assuming patients discontinue OAC after ICH (***Table 48***). Reducing the time horizon reduced the incremental QALYs, although they remained positive. Assuming patients discontinue OAC after ICH increased the incremental QALYs (i.e. favoured rivaroxaban).

Two scenarios inverted the dominance of rivaroxaban, although the ICER remained low, at between CHF864.33 and CHF23,287.87 per QALY gained (***Table 48***).

Table 48 ICER outcomes from the scenario analyses for rivaroxaban vs VKA

Scenario	Incremental costs (CHF)	Incremental QALYs	ICER
Base case	–1,209.94	0.283	Dominant
Tim horizon: 5 years	–533.62	0.030	Dominant
Time horizon: 10 years	–1,106.87	0.106	Dominant
Discontinue OAC after ICH [a]	–3,031.44	0.434	Dominant
Start age: 60 years	–3,470.20	0.336	Dominant
Start age: 80 years	–10.10	0.198	Dominant
No long-term disutility after stroke (i.e. IS or ICH)	–1,209.94	0.268	Dominant
Include long-term stroke costs [b]	–3,640.65	0.283	Dominant
Include additional costs for acute stroke events	–3,022.53	0.283	Dominant
No VKA monitoring costs [c]	6,594.57	0.283	CHF23,287.87/QALY gained
No increased mortality risk after ICH	–1,484.00	0.270	Dominant
No increased event risk after any previous IS or ICH	228.94	0.265	CHF864.33/QALY gained
Discount rate: 0%	–1,371.84	0.406	Dominant
Discount rate: 6%	–1,059.53	0.204	Dominant

Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **ICH**: intracranial haemorrhage; **IS**: ischaemic stroke; **OAC**: oral anticoagulation; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.

Notes:
[a] For patients with a history of ICH, hazard ratios reflecting the relative effect of no treatment in comparison to VKAs were applied. These hazard ratios are summarised in ***Table 126, Appendix D***)
[b] An arbitrary value of CHF5,000 per 3-month cycle was assigned to patients with a history of IS, ICH, or IS & ICH.
[c] Monitoring costs for patients on VKA were set equal to those for patients on DOAC (i.e. 2.5 GP visits per year).

8.2.6.4.5 NRSI evidence for relative efficacy estimates

The incremental cost-effectiveness of rivaroxaban vs VKAs based on relative efficacy estimates from the NRSI meta-analysis is presented in ***Table 49***. Over a lifetime horizon, rivaroxaban resulted in cost savings but resulted in less QALYs lived in comparison to VKAs.

Table 49 Incremental cost effectiveness of rivaroxaban based on NRSI relative effects

	Cost per patient (CHF)	Incremental cost (CHF)	QALYs per patient	Incremental QALYs	ICER (CHF per QALY gained)
Rivaroxaban	29,338.44	–2,812.64	6.726	–0.431	NA
VKA	32,151.08	NA	7.157	NA	6,522.94

Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.

One-way DSA and PSA were undertaken to provide decision-makers information on the key model drivers and overall certainty of the outcome (***Section 17.4.3, Appendix D***).

The frequency of INR testing was the most influential driver of incremental costs (***Figure 61, Appendix D***). Toward the upper bound of this variable (frequency: 30 days), incremental costs inverted from negative to positive (i.e. in favour of VKA). The relative effect of rivaroxaban with respect to all-cause mortality was the most influential driver of incremental QALYs; however, incremental QALYs remained negative (i.e. favoured VKA) across the full uncertainty range of the variable (***Figure 62***, ***Appendix D***).

NRSI-based analysis findings disagreed with results of the RCT-based analysis, which indicated with a high degree of certainty that rivaroxaban was cost-effective over VKAs beyond a WTP of around CHF10,000 (***Figure 52***). The majority of PSA iterations from the NRSI-based analysis fell in the western quadrants of the CE plan, indicating a high probability rivaroxaban is associated with fewer QALYs lived than VKA (***Figure 63, Appendix D***). The largest portion of PSA iterations fell in the south-west quadrant (i.e. rivaroxaban less costly and less effective than VKA). From the CEAC curve, it is apparent that, beyond a WTP threshold of CHF20,000, VKAs have close to a 100% probability of being cost-effective over rivaroxaban (***Figure 64, Appendix D***).

8.2.7 Findings: budget impact

The number of anticoagulated AF patients in Switzerland in 2021 was estimated (***Section 8.2.7.1***) and this estimate extrapolated over the period 2022 to 2026 (***Section 8.2.7.2***). The budget impact of DOACs over the period 2022 to 2026 was explored under current policy conditions (***Section 8.2.7.3***). The clinical and economic evidence presented in this HTA did not provide justifications to model the financial implications of any policy changes (i.e. a restriction of disinvestment from DOACs). Therefore, no potential policy changes have been considered.

8.2.7.1 Number of treated NVAF patients in Switzerland currently

To estimate the number of anticoagulated patients with NVAF in Switzerland, an epidemiological approach was utilised, requiring the following estimates:

- size of the adult (≥18 years) population in Switzerland
- prevalence of NVAF in the adult population
- proportion of adult NVAF patients receiving OAC therapies
- market share of DOACs vs VKAs.

Epidemiological data informing these estimates described AF cohorts rather than NVAF specifically; therefore, subsequent sections use the term AF rather than NVAF. The term NVAF excludes patients with moderate/severe mitral stenosis or a mechanical prosthetic heart valve(s) but not all AF patients with valvular heart disease (***Section 5.1***). Patients with moderate-to-severe mitral stenosis or a mechanical prosthetic heart valve require anticoagulation with VKAs; DOACs are contraindicated or not recommended.[62]

Sources for each of these parameters and the estimated number of anticoagulated AF patients in Switzerland in 2021 derived using the epidemiological approach are provided in ***Table 50***. Based on these calculations, approximately 168,032 patients in Switzerland were anticoagulated due to AF in 2021.

Table 50 Epidemiologically estimated number of anticoagulated Swiss AF patients, 2021

Parameter	Value	Data sources
Adult population (≥18 years of age)	7,208,805	Federal Statistics Office[192]
Adult population with AF	199,562	The prevalence of AF was informed by age- and gender-specific prevalence rates from a German cohort of 8.3 million persons.[193]
Anticoagulated AF patients	168,032	The proportion of anticoagulated AF patients was informed by pooled data from 2 Swiss cohort studies (BEAT-AF and Swiss-AF).[166]
• DOAC	• 116,449 ***(69.3%)***	The proportion of anticoagulated AF patients treated with DOAC (vs VKA) was informed by IQVIA survey data (study period April 2021 to March 2022)[178]
• VKA	• 51,583 ***(30.7%)***	

Abbreviations:
AF: atrial fibrillation; **BEAT-AF**: Basel Atrial Fibrillation cohort study; **DOAC**: direct oral anticoagulant; **VKA**: vitamin K antagonist.

8.2.7.2 Projected number of treated AF patients

The epidemiological-based estimates described above were used to extrapolate over the period 2022 to 2026. Swiss population projections published by the Federal Statistics Office, which account for expected demographic changes in the Swiss population over the period, were accounted for in the population projections.[192]

For the extrapolation, a constant level of AF prevalence in all age and gender groups over the period was assumed. It was also assumed that the proportion of Swiss patients with AF who were anticoagulated would remain stable over the period. However, it was assumed that the proportion of anticoagulated AF patients in Switzerland receiving DOAC (vs VKA) would rise over the period, in line with the growth observed in the prescribing patterns of a sample of Swiss practitioners over the last 3 years (i.e. IQVIA data).[178]

IQVIA data for the period April 2019 to March 2022 points toward continued growth in the relative use of DOACs (vs VKAs). For the period April 2019 to March 2020, the data showed that 61.7% of OAC prescriptions written for patients with a diagnosis of AF or atrial flutter (i.e. ICD-10 code I48) were for DOAC (vs 38.3% for VKA).[178] This estimate grew in the following 2 years to 68.8% between April 2020 and March 2021, and further to 69.3% between April 2021 and March 2022. Growth in the relative use of DOACs is aligned with European guidelines, which recommend DOACs in preference to VKAs for stroke prevention in patients with AF.[86]

The projected number of anticoagulated AF patients in Switzerland over the period 2022 to 2026 is shown in ***Table 51***. The population was projected to grow from an estimated 168,032 patients in 2021 to 188,072 in 2026. The proportion of anticoagulated AF patients receiving DOAC was estimated to grow from 69.3% in 2021 to 92.7% in 2026, assuming an annual growth rate of 6%. Accordingly, the number of Swiss patients receiving DOAC was projected to increase from an estimated 116,449 in 2021

to 174,301 in 2026, while the number of patients receiving VKA was projected to decrease over the period (***Table 51***).

Table 51 Projected number of anticoagulated Swiss patients with AF, 2021 to 2026

	Parameter	2021	2022	2023	2024	2025	2026	Extrapolation
A	Adult population with AF	199,562	204,203	208,916	213,703	218,502	223,363	Swiss population projections.[192] Prevalence of AF informed by age- and gender-specific prevalence rates from a German cohort.[193] Assumed that age- and gender-specific prevalence would remain constant.
B	Anticoagulated AF patients	168,032	171,939	175,907	179,938	183,979	188,072	Proportion of anticoagulated AF patients informed by pooled data from 2 Swiss cohort studies (BEAT-AF and Swiss-AF).[166] Assumed that the proportion of Swiss patients with AF who are anticoagulated would remain constant.
C	% DOAC	69.3%	73.4%	77.8%	82.5%	87.4%	92.7%	6.0% p.a. growth in the proportion of anticoagulated AF patients receiving a DOAC was assumed based on recent trends seen in IQVIA survey results.[178 a]
D	AF patients receiving DOAC	116,449	126,289	136,937	148,459	160,878	174,301	B * C
E	AF patients receiving VKA	51,583	45,650	38,970	31,479	23,100	13,771	B * (1 – C)

Abbreviations:
AF: atrial fibrillation; **DOAC**: direct oral anticoagulant; **VKA**: vitamin K antagonist.
Notes:
[a] Assumed annual growth rate of 6.0% p.a. reflects the average annual growth in OAC prescriptions written for DOAC (vs VKA) among patients with a diagnosis of AF or atrial flutter over 3 years of IQVIA survey data (i.e. April 2019 to March 2022).[178] The assumed growth rate was tested in sensitivity analysis.

Estimates of the split between each DOAC and each VKA within the overarching drug classes were based on the prescribing patterns of a sample of Swiss practitioners over the last 3 years (i.e. IQVIA data).[178] Specifically, the average proportion of DOAC prescriptions written for apixaban (28.5%), dabigatran (2.8%), edoxaban (11.1%) and rivaroxaban (57.6%) over the last 3 years and the average proportion of VKA prescriptions written for acenocoumarol (25.9%) and phenprocoumon (74.1%) were derived. It was assumed that the proportional split within each drug class would remain constant over the extrapolation period.

The projected number of anticoagulated AF patients receiving each drug over the period 2022 to 2026 is shown in ***Table 52***.

Table 52 Projected number of patients treated with each oral anticoagulant, 2021 to 2026

Preparation	2021	2022	2023	2024	2025	2026	Calculation
DOAC							
Apixaban	33,170	35,973	39,006	42,288	45,825	49,649	Row D ***Table 51*** × 28.5% [a]
Dabigatran	3,267	3,543	3,842	4,165	4,513	4,890	Row D ***Table 51*** × 2.8% [a]
Edoxaban	12,939	14,032	15,216	16,496	17,876	19,367	Row D ***Table 51*** × 11.1% [a]
Rivaroxaban	67,073	72,741	78,874	85,511	92,664	100,396	Row D ***Table 51*** × 57.6% [a]
VKA							
Acenocoumarol	13,386	11,846	10,113	8,169	5,995	3,573	Row E ***Table 51*** × 25.9% [b]
Phenprocoumon	38,197	33,804	28,857	23,310	17,106	10,197	Row E ***Table 51*** × 74.1% [b]

Abbreviations:
DOAC: direct oral anticoagulant; **VKA**: vitamin K antagonist.
Notes:
[a] Relative utilisation of each DOAC reflects the average proportion of DOAC prescriptions written for apixaban, dabigatran, edoxaban and rivaroxaban across 3 years of IQVIA survey data (i.e. April 2019 to March 2022). [178]
[b] Relative utilisation of each VKA reflects the average proportion of VKA prescriptions written for acenocoumarol and phenprocoumon across 3 years of IQVIA survey data (i.e. April 2019 to March 2022.[178]

8.2.7.3 Projected oral anticoagulation costs

8.2.7.3.1 Projected drug costs

Projected OAC drug costs were derived using the daily cost for each active substance described in ***Section 8.2.5.3.1*** (***Table 26*** and ***Table 27***). For these estimates, full persistence among all treated AF patients was assumed (i.e. each patient incurred costs for 365 days of medication usage).

Estimated drug costs for 2021 and projected drug cost over the period 2022 to 2026 are shown in ***Table 53***. The total payer cost of OACs for patients with AF was estimated to be approximately CHF128.0 million in 2021, reflecting around 53% of total OAC costs for the year (CHF240 million; © COGE GmbH. Tarifpool. © SASIS AG sales data). Considering the average proportion of prescriptions for each OAC written for patients with AF over the 3 years between April 2019 and March 2022 observed in the IQVIA survey (43.0 to 78.7% depending on the OAC),[178] payer costs of around CHF134 million for OACs in AF are derived (see ***Table 133***, ***Appendix D***). This figure supports the base estimate of CHF128 million (***Table 53***), being only 4.8% higher.

Payer costs for OACs for AF were estimated to increase to approximately CHF188.2 million by 2026 (***Table 53***).

Table 53 Projected oral anticoagulant drug costs, 2021–2026

Preparation	2021	2022	2023	2024	2025	2026
DOAC						
Apixaban	36,441,989	39,521,339	42,853,657	46,459,439	50,345,862	54,546,439
Dabigatran	3,660,600	3,969,920	4,304,652	4,666,853	5,057,244	5,479,193
Edoxaban	13,176,447	14,289,858	15,494,735	16,798,489	18,203,716	19,722,532
Rivaroxaban	71,976,486	78,058,503	84,640,156	91,761,929	99,437,994	107,734,543
Total DOACs	125,255,523	135,839,620	147,293,200	159,686,711	173,044,816	187,482,707
VKA						
Acenocoumarol	823,155	728,482	621,885	502,341	368,633	219,751
Phenprocoumon	1,891,632	1,674,071	1,429,108	1,154,393	847,129	504,993
Total VKAs	2,714,787	2,402,552	2,050,993	1,656,734	1,215,762	724,743
Total costs						
Total	127,970,310	138,242,172	149,344,193	161,343,444	174,260,578	188,207,450

Abbreviations:
DOAC: direct oral anticoagulant; **VKA**: vitamin K antagonist.

8.2.7.3.2 Projected monitoring costs

Projected monitoring costs were derived using the assumptions and unit costs described in ***Section 8.2.5.3.2***. Estimated monitoring costs for 2021 and projected monitoring cost over the period 2022–2026 are shown in ***Table 54***. Total monitoring costs were estimated at approximately CHF88.4 million in 2021, decreasing to CHF44.7 million in 2026. This decrease was driven by reducing costs of VKA monitoring (CHF71.3 million in 2021 reducing to CHF19.0 million in 2026). In 2021, 80.6% of monitoring costs were attributed to VKA use, while only 69.3% of patients were assumed to be treated with VKA. In 2026, the proportion of monitoring costs attributed to VKA use had reduced to 42.5%.

Table 54 Projected monitoring costs associated with oral anticoagulant use, 2021–2026

Preparation	2021	2022	2023	2024	2025	2026
DOAC						
Apixaban	4,895,861	5,309,561	5,757,247	6,241,672	6,763,800	7,328,134
Dabigatran	482,178	522,922	567,013	614,723	666,145	721,725
Edoxaban	1,909,799	2,071,177	2,245,812	2,434,779	2,638,453	2,858,591
Rivaroxaban	9,900,037	10,736,590	11,641,867	12,621,434	13,677,242	14,818,394
Total DOACs	17,187,874	18,640,251	20,211,939	21,912,608	23,745,640	25,726,843
VKA						
Acenocoumarol	18,490,201	16,363,597	13,969,153	11,283,883	8,280,458	4,936,170
Phenprocoumon	52,762,986	46,694,582	39,861,881	32,199,289	23,628,823	14,085,680
Total VKAs	71,253,187	63,058,179	53,831,033	43,483,172	31,909,282	19,021,850
Total costs						
Total	88,441,062	81,698,429	74,042,972	65,395,780	55,654,922	44,748,693

Abbreviations:
DOAC: direct oral anticoagulant; **VKA**: vitamin K antagonist

8.2.7.3.3 Projected treatment costs

Estimated total treatment cost (i.e. drug and monitoring costs combined) for 2021 and projected total treatment costs for the period 2022 to 2026 are summarised in ***Table 55***.

Table 55 Projected oral anticoagulant treatment costs (drug and monitoring), 2021–2026

Drug class	2021	2022	2023	2024	2025	2026
Total DOACs	142,443,397	154,479,871	167,505,140	181,599,318	196,790,456	213,209,550
Total VKAs	73,967,974	65,460,731	55,882,026	45,139,905	33,125,043	19,746,593
Total	216,411,371	219,940,602	223,387,166	226,739,224	229,915,500	232,956,143

Abbreviations:
DOAC: direct oral anticoagulant; **VKA**: vitamin K antagonist

8.2.7.4 Sensitivity analysis

Some of the key assumptions used in the budget impact analysis are uncertain, including the estimated number of oral anticoagulated AF patients, the proportion of anticoagulated patients treated with DOACs (vs VKAs), the future price of DOACs and the assumed growth in the relative use of DOACs under current policy conditions.

Alternative assumptions regarding these parameters were explored in a sensitivity analysis, the results of which are summarised in ***Table 56***. Projected treatment costs for the year 2026 were most sensitive to the estimated number of anticoagulated AF patients, followed by the assumed future cost of DOACs. Projected OAC drug costs were most sensitive to the assumed growth rate in the relative use of DOACs (vs VKAs).

Overall, the sensitivity analyses suggest that total OAC drug costs for stroke prevention in AF may be between CHF148.5 million and CHF225.8 million in 2026, under current policy and practice conditions (***Table 56***).

Table 56 Projected treatment costs for the sensitivity analyses conducted

Scenario	2021	2022	2023	2024	2025	2026
Anticoagulated AF patients, low (–20%)						
Total treated patients	134,425	137,551	140,726	143,951	147,183	150,457
DOAC patients	93,159	101,031	109,550	118,768	128,703	139,441
VKA patients	41,266	36,520	31,176	25,183	18,480	11,016
Drug costs	102,376,248	110,593,738	119,475,355	129,074,755	139,408,462	150,565,960
Total treatment costs	173,129,097	175,952,482	178,709,733	181,391,379	183,932,400	186,364,914
Anticoagulated AF patients, high (+20%)						
Total treated patients	201,638	206,327	211,089	215,926	220,774	225,686
DOAC patients	139,739	151,547	164,325	178,151	193,054	209,161

Scenario	2021	2022	2023	2024	2025	2026
VKA patients	61,899	54,780	46,764	37,775	27,720	16,525
Drug costs	153,564,371	165,890,607	179,213,032	193,612,133	209,112,693	225,848,940
Total treatment costs	259,693,645	263,928,722	268,064,599	272,087,069	275,898,600	279,547,371
Proportion receiving DOAC, high (85.4%) [a]						
Total treated patients	168,032	171,939	175,907	179,938	183,979	188,072
DOAC patients	143,512	155,639	168,761	172,741	176,619	180,549
VKA patients	24,520	16,300	7,146	7,198	7,359	7,523
Drug costs	155,655,394	168,266,648	181,900,240	186,183,196	190,363,606	194,598,805
Total treatment costs	210,707,976	213,755,269	216,680,305	221,621,994	226,598,120	231,639,462
Growth rate, low (0.8% p.a.) [b]						
Total treated patients	168,032	171,939	175,907	179,938	183,979	188,072
DOAC patients	116,449	120,079	123,801	127,618	131,493	135,459
VKA patients	51,583	51,860	52,106	52,320	52,485	52,613
Drug costs	127,970,310	131,889,368	135,906,012	140,022,886	144,199,831	148,472,116
Total treatment costs	216,411,371	221,249,341	226,155,561	231,131,465	236,108,305	241,142,006
Cost DOACs, low (-20% for all DOACs)						
Total treated patients	168,032	171,939	175,907	179,938	183,979	188,072
DOAC patients	116,449	126,289	136,937	148,459	160,878	174,301
VKA patients	51,583	45,650	38,970	31,479	23,100	13,771
Drug costs	102,919,205	111,074,248	119,885,553	129,406,102	139,651,615	150,710,909
Total treatment costs	191,360,267	192,772,678	193,928,526	194,801,882	195,306,536	195,459,601

Abbreviations:
AF: atrial fibrillation; **DOAC**: direct oral anticoagulant; **VKA**: vitamin K antagonist.
Notes:
[a] A ceiling of 96.0% was placed on the proportion of OAC-treated patients that could receive a DOAC.
[b] In the base case, the assumed growth rate in the relative use of DOACs (6.0% p.a.) was based on the average annual growth rate in the relative proportion of DOAC (vs VKA) prescriptions for patients with a diagnosis of AF or atrial flutter over the last 3 years from IQVIA survey results. The assumed rate used in the sensitivity analysis (0.8% p.a.) was instead based on the growth rate over the last 2 years.

9 Legal, social, ethical and organisational issues

Summary statement ethical, legal, social and organisational issues

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A total of 21 studies relevant to the ELSO domains were identified from systematic and targeted, non-systematic keyword searches.

No legal issues were identified.

Social issues associated with DOAC use include patient-related, physician-related and healthcare system-related factors that affect adherence (i.e. the extent to which a patient conforms to their prescribed therapy in terms of timing, dosage and frequency) and persistence (i.e. the period of time from initiation of therapy to discontinuation) to DOAC and VKA therapies. These are common issues related to both VKA and DOAC use, as under-treatment can result in clotting events and over-treatment can result in bleeding events. Regarding the relative benefits of each treatment, there were no data on adherence. The RCT and NRSI evidence either demonstrated improved or no difference in persistence for DOACs compared to VKAs.

An ethical issue associated with DOAC use relates to the benefit/harm profile. Although a favourable benefit/harm profile of DOACs was demonstrated from the RCT evidence, the real-world effectiveness data were difficult to interpret. Based on the lack of adherence and persistence data from NRSIs, there is a fundamental issue of how treatment effectiveness of DOACs is monitored in practice; in contrast, VKAs require regular follow-up of INR monitoring.

In relation to organisational impacts on practice, DOACs have significantly fewer monitoring requirements compared to VKAs, which require INR testing approximately every 20 days. At-home INR self-testing could potentially reduce the cost and the intensity of clinician involvement in VKA therapy, but it is unclear how effective these tests are, how much they cost, or how widely available they are in Switzerland.

9.1 Methodology: ethical, legal, social and organisational issues

The systematic literature searches outlined in ***Section 7.1.1*** and ***Appendix A*** were used to identify studies relevant to the legal, social, ethical and organisational issues related to DOAC and VKA use in patients with NVAF. In addition, one reviewer conducted targeted, non-systematic keyword searches for literature addressing these domains using the terms ‘atrial fibrillation’ and ‘anticoagulation’. Relevant studies from 2010 were included, given this represents the period after which pivotal trials of OAC for

stroke prevention were published.[81] Identified studies were selected by one reviewer and checked by a second reviewer for information on legal, social, ethical and organisational issues or consequences regarding the prescription of OAC therapy.

9.2 Results: legal, social, ethical and organisational issues

A total of 21 studies were relevant to the social, ethical and organisational domains. No studies evaluated legal issues. The included studies consisted of 12 reviews (systematic and/or narrative) and 9 observational studies. Evidence tables summarising the study design, study aim and main outcomes grouped by themes are presented in ***Appendix D***. Studies have not been separated according to domain, because there was substantial overlap between the included studies and the ethical, social and organisational domains.

9.2.1 Findings: social issues

Findings on the social issues were synthesised narratively according to several prominent themes, including patient knowledge and understanding of AF and OAC therapy (i.e. trajectory of AF and its associated risks), patient experiences with healthcare providers, and patient characteristics related to AF as a medical condition.

9.2.1.1 Patient knowledge and understanding of AF and OAC therapy

In studies evaluating the value of OAC medication according to risk attributes, stroke avoidance was valued by many patients.[54,194-200] When considering other trade-offs such as risk of bleeding, patients accepted serious bleeds to avoid stroke.[54,198,201,202] However, there was substantial variability in the threshold number of bleeds observed for OAC acceptance. For instance, Sharfin et al 2016 observed that patients were willing to pay 2 times more per month in medication cost for every 1% reduction in stroke risk compared to bleed risk,[198] whereas Wilke et al 2017 described a survey that showed AF patients valued a 1% increased risk of a fatal bleeding event the same as a 2% increase in non-fatal MI, a 3% increase in non-fatal stroke risk and so forth.[199]

Patients were also found to have various misconceptions about AF and poor understanding of the aims of OAC therapies.[197,200,203,204] As a result, patients were less likely to recognise the physical and psychosocial impact of disease burden on lifestyle. These misunderstandings were likely caused by the patient's own health and medication beliefs, level of health literacy, degree of individualised decision-making in therapy management and contradictory recommendations made by other patients, caregivers and healthcare providers.[197]

9.2.1.2 Patient demographics and preferences for OAC therapy

Six review authors found that non-adherence to OAC was commonly seen in those of younger age (e.g. less than 75 years) and those of lower socioeconomic status or poor health literacy, whereas higher adherence rates were frequently seen among women and those of higher socioeconomic backgrounds.[54,194,195,205,206] However, conflicting results were also reported on the effect that sex and age may have on OAC treatment preferences.[54] Similarly, these health determinants were potentially influenced by medication concordance, health and medication beliefs, level of health literacy, awareness of health risks and the impact of overall burden of treatment.[54,194,195,203,205]

Other commonly reported reasons influencing adherence and utilisation of OAC were other medical conditions (e.g. psychiatric disorders), the presence of comorbidities, and lack of structured support from healthcare professionals, family or carers.[54,194,195,202,203,207] Lesser-known reasons contributing to OAC adherence included the impact of cultural beliefs and familial attitudes, along with poor social situations and geographical settings (e.g. rural location).[54]

9.2.1.3 Response to clinical evidence

Given the complexity of risks and benefits with OAC, 6 reviews focused on identifying strategies to improve adherence rates amongst patients in the primary care setting and to increase the uptake of guideline-directed thromboprophylaxis amongst healthcare providers.[208] Interventions covered computerised decision support or risk assessment tools, shared decision-making tools, guideline/protocol implementation and prescribing patterns. Interventions focused on AF treatment options, medication administration (e.g. dosing, safety) and coordinated healthcare practices.[209]

9.2.1.4 Patient opinions and attitudes

Healthcare providers were influenced by patients' characteristics, opinions and attitudes when considering OAC therapy. Demographic factors such as age, level of cognitive impairment, mobility restrictions and fall risk were known to influence OAC prescribing practices or preclude the initiation of guideline-adherent therapy. Clinicians also acknowledged the burden of medication costs, INR testing and dose variations, given their potential impact on patients in poor health or those who might struggle with access to medical care.

9.2.1.5 Medication-related factors

Patients and healthcare providers both offered similar insights into the factors driving choice of OAC therapy. Studies reported on diverse medication-related variables such as access, adherence, adjustments, administration, adverse events, costs, delivery, interactions, knowledge, location, maintenance, restrictions and safety.[54,194,198,202,203,205,207,210-213] The factors most valued by patients when

considering OAC therapy included dosing frequency, antidote availability, absence of dietary restrictions and/or drug interactions, and ease of access.

9.2.1.6 Cost of medication

Multiple authors described patients as being sensitive to drug costs, which made cost a prescribing factor in eligible NVAF patients.[195,198,202,207,212] The out-of-pocket costs to patients were often driven by socioeconomic determinants such as sex (female), education, employment status, income, ethnicity and geographical region.[205]

9.2.2 Findings: ethical issues

The main ethical issue associated with the use of DOACs and VKAs for the treatment of NVAF relates primarily to the relative benefit/harm profile of the drugs; fundamentally, this overlaps with social and organisational domains regarding the follow-up requirements of each drug.

9.2.2.1 Benefit/harm balance

As noted previously, patients value therapies that reduce their risk of stroke and other clinical events.[54,194-200] The RCT evidence identified in this HTA has demonstrated a favourable benefit/harm profile for DOACs; however, the results from the NRSIs are less clear. The importance of demonstrating the safety and effectiveness of DOACs and VKAs in practice is closely related to their follow-up requirements. In a trial setting, patients are followed closely by investigators with regular follow-up at defined intervals. In such settings, measured treatment adherence and persistence may not reflect real-world practice. The NRSIs included in this HTA did not report adherence, and they reported variable persistence rates relative to VKAs based on data at a high risk of confounding. In the absence of high quality data on the adherence and persistence of patients to VKAs and DOACs in real-world settings, the frequency of contact between patients and their treating physician is an important factor to consider when considering the relative benefit/harm balance of the drugs in practice.[194,195,206,212]

9.2.3 Findings: organisational domains

Findings on the organisational aspects focused on the type of clinical setting (e.g. institution, specialised clinic) in which adherence or persistence was measured, and follow-up requirements of DOACs compared to VKAs.

9.2.3.1 Healthcare infrastructure

Patient management through specialised anticoagulation clinics for warfarin dosing showed lower rates for non-persistence compared with studies without anticoagulation clinics.[207,211] While there was no explicit requirement for monitoring DOACs, there was preliminary evidence showing a trend for patients followed in university-hospital settings to have higher non-persistence than patients treated in local

community settings.[195,212] This was directly related to the type of treating clinician in these settings and associated patient contact patterns for appropriate disease management.

9.2.3.2 Patient follow-up requirements for DOACs and VKAs

Five studies described INR monitoring as a factor influencing a patient's decision around VKA use.[195,197,200,208,212] While some patients felt the frequency of INR monitoring to be burdensome, there was a subset who preferred the assurance INR monitoring could provide in recognising stroke risk.[197,212] Costs related to INR monitoring were also suggested to influence adherence.[198] Other factors that concerned patients included the daily management of VKA (e.g. need for dietary restrictions, awareness of drug interaction) and the potential limitations placed on activities such as sport.[197]

9.2.3.3 INR self-testing

As noted in the cost-effectiveness analyses, routine lab-based INR monitoring and clinician follow-up was a driver for the relative cost-ineffectiveness of VKAs compared to DOACs. At-home self-testing and self-management has been used in Switzerland since at least 2007, and may offer an alternative to lab-based INR monitoring.[214] These devices offer patients the ability to determine the dose of VKA on the basis of capillary INR, with dose adjustment indicated by dose adaptation tables.[214] A small trial in Switzerland (n=35) demonstrated favourable results, with 75% of patients maintaining INR in the therapeutic range over a 12-month period, with high patient satisfaction.[214] However, there are several considerations around the implementation of self-testing and self-management, including training and education requirements of patients, the necessity of providing a patient support hotline, the diagnostic accuracy of the devices, device failures and the relative costs compared to lab-based monitoring with clinician follow-up; these factors will affect the viability of INR self-testing.[214]

10 Additional issues

10.1 Clinical practice position statements and guidelines

Clinical practice guidelines were sought to inform what recommendations are made regarding the use of DOACs and VKAs for the treatment of NVAF in countries with similar levels of economic development to Switzerland. In total, 7 clinical practice guidelines were identified through the systematic search and targeted non-systematic searches (summarised in ***Table 135***, ***Appendix F***). The issuing organisations were from the Asia-Pacific region, Australia, Canada, Europe, the UK and the USA. One guideline did not have an applicable jurisdiction.

Only recommendations pertaining to specific OACs were included. General guidance for detection, monitoring and therapy, or guidance that did not distinguish between different OACs was excluded.

All guidelines recommended the use of OAC (VKA or DOAC) for patients with AF at risk of stroke, based on CHA_2DS_2-VASc score.[4,8,215-219] Where reported, guidelines recommend patient-centred strategies for shared decision-making, and to encourage and monitor adherence.[4,8,215,216,219] The guidelines are consistent in recommending DOACs in preference to VKA, unless contraindicated. All guidelines recommended VKA for patients with moderate to severe mitral stenosis or mechanical heart valves.

In terms of the use of VKA and warfarin, 2 guidelines suggested the SAMe-TT_2R_2 score to aid decision-making and help identify patients likely to do well on VKA.[217,218] Where mentioned, guidelines recommended point-of-care INR measurement in the management of patients receiving warfarin (***Table 135***).[4,8,216,218,219]

Five guidelines recommended the use of DOAC in patients unable to maintain a therapeutic INR level with VKA, together with the option of education or counselling to improve the time in therapeutic range (TTR).[4,8,217-219]

Guidelines provided varied recommendations and suggestions for various subpopulations. For patients with AF and coronary artery disease, there is some disagreement. Three guidelines recommended DOAC in preference to VKA,[4,215,217] and one guideline suggested either a DOAC or adjusted dose VKA therapy.[218] For patients with chronic kidney disease, 3 guidelines recommended VKA or the cautious use of selected DOACs, depending on creatinine clearance or stage of the disease.[8,216,218]

For pregnancy and breast-feeding, 2 guidelines recommended or suggested the use of VKA or avoidance of DOACs.[4,218] Guidelines varied in the detail provided on the use of OAC after cardioversion, acute IS, ICH or AF ablation. In all cases (3 guidelines), DOACs were preferred over VKA.[4,218]

10.2 Ongoing clinical trials and studies

Ongoing and unpublished clinical trials and non-randomised studies (k=11) meeting the PICO criteria are summarised in ***Table 136*** (***Appendix F***). Unpublished RCTs or NRSIs with a published actual or anticipated study completion date of or prior to 2017 were excluded, as these are likely to remain unpublished.

The included RCTs (n = 2) and NRSIs (n = 9) are registered in the US, Germany, the Netherlands, Australia, Japan and the UK. Five RCTs were not included as they were from non-stratum A countries and their results are unlikely to represent outcomes in Switzerland.[220-224] One of these RCTs was in a population of patients with AF and rheumatic heart disease.[222]

Of the RCTs and NRSIs shown in ***Table 136***, 3 are recruiting or not yet recruiting and do not have published expected completion dates (NTR6721, ACTRN12616, JPRN-UMIN00). One NRSI has an estimated completion date of December 2022. All other RCTs and NRSIs appear to be recently completed, although the results are yet to be published.

The RCTs and NRSIs are in the broad population of AF or NVAF and will add to the current body of evidence. Five are investigating defined subsets of patients with AF: 3 NRSIs have a population of frail elderly patients (NCT04878497, NTR6721, ACTRN12616000452493); 2 RCTs have patients with heart failure or acute coronary syndrome (JPRN-UMIN00-0021649, EUCTR2015-005566-33-DE).

The RCTs and NRSIs all compare DOAC and VKA. One RCT and one NRSI compare DOAC with phenprocoumon; one NRSI compares DOACs with an unspecified VKA. The other RCTs and NRSIs specifically compare DOACs with warfarin. The majority of the identified NRSIs are investigating the real-world use of OACs in large populations, generally through data obtained from electronic healthcare databases. The results of these studies will further inform the effectiveness of these medications in clinical practice, outside the formal reporting of efficacy in RCTs.

A number of additional trials/studies were identified comparing different OACs in a range of specific populations of patients with AF. These have not been summarised here. They include the following patients:

- those with mitral stenosis (k = 4)
- those taking anticoagulation after previous stroke TIA or haemorrhage (k = 3)
- those after cardiac surgery, percutaneous coronary intervention or catheter ablation (k = 12)
- those after ablation for AF (k = 4)
- those with chronic kidney disease undergoing haemodialysis (k = 4)
- those after transcatheter aortic valve implantation (k = 1)
- those after mitral valve replacement (k = 1).

11 Discussion

11.1.1 Comparison to existing SRs and HTA reports

In its assessment of benefits and harms, the NICE evidence review committee concluded that DOACs were superior compared to warfarin, although the magnitude of the effects were small and not necessarily clinically important.[58] The Lopez-Lopez NMA reported similar effects.[44] Notably, both reviews attempted to investigate the relative ranking for DOAC therapies, which was explicitly outside the scope of our report. The NICE evaluation committee recommended that first-line OACs should be any DOAC (apixaban, edoxaban, dabigatran or rivaroxaban), without any differentiation between them, and for the final decision to be made between the clinician and the patient, considering risk factors and preferences.[58]

The results of the current HTA closely align to the NICE report and the Lopez-Lopez NMA. This is unsurprising, as no new RCTs published after the search dates in the NICE report were identified and a subset of the overall evidence included in the NICE review was investigated. The results of the current HTA reinforce the overall conclusions found in the NICE review and provide new, albeit limited, information from NRSIs.

11.1.2 Comparison to existing economic literature

The cost-effectiveness of DOACs relative to VKAs is a well-studied area. A total of 55 relevant economic evaluations published within the context of WHO Mortality Stratum A countries since 2013 were identified (see ***Section 8.2***). To facilitate a comparison of these results with the wider evidence base, a selection of evaluations performed from the perspective of Switzerland or a neighbouring country (Austria, France, Germany, Italy), plus the *López-López model* and the NICE update of this model, were considered. Results data from these evaluations are summarised in ***Table 132*** (***Appendix D***).

The *López-López model* was developed to evaluate the most cost-effective first-line OAC for patients with AF from the perspective of the UK National Health Service (NHS).[44,158,159] At WTP thresholds of £20,000 and £30,000, all DOACs were found to have a positive expected incremental net benefit (INB) compared with VKAs; however, apixaban had the highest probability of being the most cost-effective option from all OACs considered. Based on expected costs and QALYs for each DOAC and VKA, apixaban, dabigatran and edoxaban showed dominance over VKAs, while rivaroxaban was cost-effective. In an update undertaken for NICE in 2021, similar results were observed (see ***Table 132***, ***Appendix D***).[58]

From an Austrian payer's perspective, a recent adaptation of the *López-López model* found apixaban to be cost-effective over VKAs.[100] Expected per-patient lifetime costs associated with clinical events were

lower for apixaban; the greatest savings generated by reductions in major bleeds and ICHs. However, additional drug costs were not completely offset. The key model driver was the relative effect of apixaban on all-cause mortality. At its upper bound, apixaban was no longer cost-effective.[100] Similarly, the relative efficacies of each DOAC with respect to all-cause mortality was found to be the key model driver in all 4 pairwise comparisons; however, DOACs remained dominant or cost-effective across the uncertainty ranges of these inputs in one-way DSAs, except for towards the upper bound of the relative efficacy estimate for rivaroxaban.

From an Italian payer's perspective, another recent adaptation of the *López-López model* sourcing measures of effect from an independent NMA of real-world evidence found all DOACs to be dominant over VKAs.[153] Key model drivers were the relative effect of DOACs on all-cause mortality and DOAC drug costs; however, DOACs remained dominant in all one-way DSAs. Expected per-patient lifetime monitoring costs were €12,163 for VKAs compared with between €2,106 and €2,730 for the DOACs, while expected lifetime drug costs were €184 compared with between €5,777 and €6,933. Trends in the expected cost outcomes align with the findings of this HTA (i.e. considerably higher monitoring costs with VKAs) and could begin to explain the robust dominance observed.

From a Swiss payer's perspective, an adaptation of the *Sorensen model* found dabigatran to be cost effective over VKAs.[140] The largest effect of dabigatran was strong reductions of HS and ICH relative to VKAs.[140] Adaptations of the *Sorensen model* to the French and Italian payers' perspectives, similarly found dabigatran to be cost effective relative to VKAs (see ***Table 132***, ***Appendix D***).[108,109,121] Key drivers were the relative effect of dabigatran on IS and the model time horizon.[108,121] From a French payer's perspective, use of real-world rather than RCT data improved the cost-effectiveness of dabigatran.[109] Notably, use of real-world cost data considerably increased the annual costs of VKA monitoring, from €134.04 to €1,011.05.[109]

Additional economic evaluations from the Italian payer's perspective found all 4 DOACs to be cost-effective over VKAs, with high probability; however, results from the German payer's perspective varied.[112-114,119,120] The *Mensch model* found rivaroxaban to be cost-effective relative to VKAs; however, results of the Krejczy et al 2014 and Krejczy et al 2015 evaluations were less favourable toward DOACs (see ***Table 132***, ***Appendix D***).[112-114] Low expected per-patient lifetime costs for VKAs and small incremental QALYs gained with DOAC use could explain the unfavourable results. Notably, the annual cost of VKA therapy (including drug and monitoring costs) was €153 (unit cost per INR monitoring episode of €0.64, with an assumed interval between testing of 3 weeks).[113] Despite the assumed interval between testing aligning with the assumption of this HTA, the unit cost for INR monitoring was considerably lower. The added costs of VKA monitoring were found to be a significant driver of economic outcomes, the dominance of all DOACs being reverted when the additional monitoring costs were

removed. Nevertheless, even under these scenarios, DOACs remained cost effective in pairwise comparisons.

A difference between the existing evidence base and the results of this HTA is that use of NRSI evidence generally (except for dabigatran) favoured VKAs rather than DOACs. From an Italian payer's perspective, adaptation of the *López-López model* updated with real-world relative efficacy estimates, found all DOACs were dominant over VKAs.[118] This difference is likely explained by differences in relative efficacy inputs, particularly the relative effect of DOACs on all-cause mortality. In the Italian model, apixaban, dabigatran and rivaroxaban reduced the risks of all-cause mortality, IS and ICH relative to VKAs. In contrast, in the NRSI-based model of this HTA, rivaroxaban was associated with a significant increased risk of all-cause mortality, while apixaban and dabigatran were associated with uncertain effects (higher or equivalent [i.e. HR of 1.00] point estimates but with 95% CIs that crossed the null). These differences were reflected in the economic findings.

11.2 Limitations in the clinical evidence evaluation

The results of this HTA report should be interpreted with an understanding of the limitations in the chosen methodology.

Firstly, study selection was split between 2 reviewers, instead of being completed in duplicate. This was necessary given the size of the literature searches and the time constraints of the project. Consequently, the risk that relevant studies were missed is higher than if the total sample had been screened in duplicate with 2 reviewers. The risk of missing studies was mitigated by implementing training samples and IRR calculation, and screening the reference lists of existing reviews on the topic.

Secondly, warfarin was used as a substantially equivalent substitute for phenprocoumon and acenocoumarol for the RCT analysis, which may have introduced applicability issues into the analysis. This decision was made in consultation with the FOPH and was based primarily on the absence of RCT evidence for phenprocoumon and acenocoumarol.

Thirdly, while not a limitation in the review methodology per se, the aim of this HTA was to compare individual DOACs against the VKA class of drugs. As such, the results do not inform a head-to-head comparison between DOACs and should not be interpreted as such. The Lopez-Lopez review conducted an NMA to address this question, but this approach remains a debated topic due to heterogeneity between the trials that may invalidate the transitivity assumption needed to conduct a robust NMA.[225]

Fourthly, the RR analyses of NRSIs included a mixture of studies that adjusted for confounding (e.g. propensity score matching), as well as studies that reported crude event numbers or event rates.

Consequently, the results of the RR analyses are at a higher risk of bias compared to the HR analyses, for specific outcomes.

Fifthly, the NRSIs that reported HRs often did not report the total event numbers in the analysis, or the event numbers were unclear. Thus, it was not possible to estimate the absolute treatment effects in those analyses, and therefore the clinical relevance of those analyses is unclear.

Sixthly, the absolute treatment effects reported for the comparator arm in the GRADE tables were estimated by taking the average of the absolute risk observed in the comparator arms of the studies included for each analysis, weighted by population size. This may introduce bias in favour of studies that reported shorter follow-up durations, as there was less time for events to occur. In cases where NSRIs did not report event rates, absolute treatment effects for the comparator arm could not be calculated.

Finally, the ethical, legal, social and organisational domains are intended to highlight issues related to DOAC use, but do not represent a systematic review of these issues. The chosen approach for this HTA was based on direction from the FOPH about the relative weight of this information to inform potential changes to the reimbursement of DOAC for NVAF in Switzerland.

11.3 Limitations in the economic analysis

All economic models are a simplification of reality. Complex patient journeys are condensed and reflected as transitions through a limited number of health states. While the model for this HTA was constructed around the most important clinical outcomes within the context of OAC for AF (i.e. strokes, bleeds and all-cause mortality), it did not include all events that may be affected by OAC decisions. For example, myocardial infarctions (MIs), transient ischaemic attacks (TIAs) and heart failure episodes included in some previous models, were not included here.

Previous evaluations including these events have generally come to similar conclusions that DOACs are favoured over VKA. In the *López-López model,* which included MI and TIA, while both apixaban and dabigatran were associated with low rates of ICH, a higher rate of MI offset this benefit for dabigatran such that apixaban appeared the more cost-effective alternative.[44,158] Nevertheless, all DOACs, including dabigatran, demonstrated positive INBs compared with VKA. In an Italian adaptation of the *Sorensen model*, dabigatran demonstrated favourable cost-effectiveness relative to apixaban, despite the model structure including MI.[121] In any case, such intra-class DOAC comparisons are beyond the scope of this HTA.

Furthermore, not all AF-associated costs were accounted for. Nevertheless, those most relevant to oral anticoagulation and most likely to be affected by OAC decisions (i.e. drug, INR monitoring, bleed event

and stroke event costs [i.e. hospital and inpatient rehabilitation costs]) were captured. Apart from GP visits and INR monitoring checks, no other outpatient medical costs were considered. Home care and nursing home costs were also omitted. As such, the model is conservative given the full benefit of avoided clinical events (in terms of costs avoided) may not be captured and the interventions (i.e. DOACs) were generally associated with reduced event risks. Scenario analysis supported this, with incremental costs increasing in favour of DOACs under scenarios in which additional IS and ICH event costs were added or in which long-term management costs were assigned to patients with a history of IS and/or ICH.

The possibility of at-home self-testing and self-management of VKA therapy was not captured in the economic analysis given uncertainty in how effective or how widely available these tests are (see ***Section 9***). Nevertheless, these tests have the potential to reduce the cost and the intensity of clinical involvement in VKA therapy, and their omission may bias against VKAs. Furthermore, GP costs incorporated for INR monitoring may not be solely attributable to VKA therapy. Patients with comorbidities may benefit from regular GP visits, during which other chronic diseases may also be monitored. Attributing the entire cost of these GPs visits to the management of VKA therapy could again bias against VKAs. However, DOACs remained cost-effective in scenario analyses where the additional monitoring costs associated with VKA (vs DOAC) use were removed.

The model in this HTA assumed the same health state utilities for DOAC- and VKA-treated patients. In a few previous evaluations, these health state utilities have been reported as being important model drivers.[113,114,120] The assumption in this HTA is consistent with more recent models.[44,100,118]

Baseline risks of clinical events informing the model were taken from a large cohort of RCT-enrolled patients. While this cohort was well-aligned with the Swiss context (***Section 8.2.5.1.1***), there may still be some differences. Moreover, baseline risks reflect overarching risks for a general AF cohort; no subgroup analyses were undertaken (e.g. in patients with a high stroke risk or with poor INR control). Scenario analyses undertaken by NICE, which stratified the patient cohort by age, gender and CHA_2DS_2-VASc score, found apixaban to consistently have the highest INB across the £20,000 to £30,000 WTP range.[58] However, it was noted that in patients with high CHA_2DS_2-VASc scores, dabigatran had a probability of cost-effectiveness that was very close to that of apixaban, indicating low certainty that one is better than the other.[58]

Finally, medication adherence was not explicitly modelled in this HTA. It was implicitly assumed that medication adherence within the hypothetical model cohort aligned with that observed in clinical trials.

The BIA was limited to a projection of potential OAC treatment costs over the extrapolation period. Additional payer costs (notably, clinical event costs) were not included, given the BIA made no attempt to estimate the expected impact on payer costs of any potential policy changes.

12 Conclusions

The RCT evidence demonstrated favourable outcomes for the use of DOACs, noting that the evidence had a mixed risk of bias (ranging from low to high) and the difference between treatment effects were typically small. The NRSI evidence was difficult to interpret due to unmeasured confounding, substantial unbalanced dropouts between treatment groups, and conflicting results depending on the choice of outcome measure (i.e. HR or RR). As such, the RCT evidence was deemed to provide more reliable results and was used as the basis for the economic evaluation.

Economic evaluations informed by RCT data found all DOACs to be cost-saving compared to VKAs, while improving patient outcomes (i.e. QALYs lived). All DOACs increased drug costs relative to VKAs but were cost-saving in terms of monitoring and clinical event costs. Sensitivity analyses found the dominance of each DOAC to be robust. Favourable outcomes for the DOACs were driven primarily by small improvements in all-cause mortality and high costs associated with INR monitoring for VKAs.

Under current policy conditions, payer costs for OAC use in AF are expected to increase due to (anticipated) continued growth in the relative use of DOACs and expected demographic changes in the Swiss population.

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14 Appendix A: Search strategy and results

14.1 Systematic search summary

Table 57 Summary of biomedical bibliographic database search results

Database	Results
PubMed	5,598
Embase (OVID)	11,843
Cochrane Library – Reviews	9
EconLit (EBSCO)	4
INAHTA	0
Total	**17,454**

Table 58 Clinical trial registries search results [31 August 2022]

Source	Search terms	Results
World Health Organization (WHO), International Clinical Trials Registry Platform	Condition: "atrial fibrillation" OR NVAF AND Intervention: NOAC OR DOAC OR dabigatran OR Pradaxa OR Apixaban OR eliquis OR edoxaban OR lixiana OR Rivaroxaban OR Xarelto OR "vitamin K antagonist" OR VKA OR acenocoumarol OR sintrom OR phenprocoumon OR Macoumar OR warfarin Restriction: Date of registration: 01/01/2016 to 31 Aug 2022	216

Notes:
The WHO International Clinical Trials Registry Platform includes data from the following providers: Australian New Zealand Clinical Trials Registry, Chinese Clinical Trial Registry, ClinicalTrials.gov, EU Clinical Trials Register (EU-CTR), ISRCTN, the Netherlands National Trial Register, Brazilian Clinical Trials Registry (ReBec), Clinical Trials Registry - India, Clinical Research Information Service - Republic of Korea, Cuban Public Registry of Clinical Trials, German Clinical Trials Register, Iranian Registry of Clinical Trials, Japan Registry of Clinical Trials (jRCT), Pan African Clinical Trial Registry, Sri Lanka Clinical Trials Registry, Thai Clinical Trials Registry (TCTR), Peruvian Clinical Trials Registry (REPEC), Lebanese Clinical Trials Registry (LBCTR).

14.2 Systematic search results

Table 59 Search strategy – PubMed [29 March 2022]

No.	Query	Results
1	Atrial fibrillation[tw]	95,484
2	Auricular fibrillation[tw]	1,549
3	Atrium fibrillation[tw]	12
4	non-valvular[tw]	2,732
5	nonvalvular[tw]	5,204
6	NVAF[tiab]	1,368
7	**#1 OR #2 OR #3 OR #4 OR #5 OR #6**	**95,835**
8	New oral anticoagulant*[tw]	1,730
9	Novel oral anticoagulant*[tw]	1,411
10	Non-vitamin K oral anticoagulant*[tw]	456
11	Non-vitamin K antagonist*[tw]	1,406
12	Direct oral anticoagulant*[tw]	4,804
13	Factor XA inhibitor[mh]	5,777
14	Oral anticoagulant*[tiab]	17,178
15	DOAC*[tiab]	3,393
16	NOAC*[tiab]	3,219
17	OAC*[tiab]	6,765
18	Rivaroxaban[tiab]	6,487
19	Xarelto[tiab]	163
20	Apixaban[tiab]	4,286
21	Eliquis[tiab]	79
22	Edoxaban[tiab]	1,762
23	Lixiana[tiab]	26
24	Dabigatran[tiab]	5,519
25	Pradax*[tiab]	157
26	Prazax*[tiab]	4
27	IIa inhibitor*[tiab]	129
28	thrombin inhibitor*[tiab]	4,963
29	Xa inhibitor*[tiab]	2,870

30	10a inhibitor*[tiab]	81
31	direct coagulation[tiab]	32
32	antithrombin*[tiab]	17,214
33	anti-thrombin*[tiab]	871
34	**#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR # 33**	**119,034**
35	Vitamin-K antagonist*[tw]	8,360
36	VKA[tiab]	2,274
37	Phenprocoumon[tiab]	907
38	Phenprocumon[tiab]	5
39	Acenocoumarol[tiab]	1,049
40	Acenocumarol[tiab]	117
41	Warfarin[tiab]	26,411
42	**#35 OR #36 #37 OR #38 OR #39 OR #40 OR #41**	**33,996**
43	English[la]	29,089,230
44	French[la]	761,907
45	German[la]	894,554
46	Italian[la]	307,907
47	**#43 OR #44 OR #45 OR #46**	**31,024,962**
48	Animals[mh]	25,277,367
49	Humans[mh]	20,298,168
50	**#48 AND #49**	**20,298,168**
51	**#48 NOT #50**	**4,979,199**
52	editorial[pt]	599,629
53	letter[pt]	1,174,085
54	news[pt]	211,695
55	congress[pt]	82,028
56	**#52 OR # 53 #54 OR #55**	**2,062,657**
57	**(#7 AND #34 AND #42 AND #47) NOT 51 NOT #56**	**5,598**

Table 60 Search strategy – Embase (OVID) [29 March 2022]

No.	Query	Results
1	Atrial fibrillation.mp.	173,925
2	Auricular fibrillation.mp.	432
3	Atrium fibrillation.mp.	86,512
4	non-valvular.mp.	6,227
5	nonvalvular.mp.	4,188
6	NVAF.tw.	2,834
7	**1 or 2 or 3 or 4 or 5 or 6**	**199,046**
8	New oral anticoagulant*.mp.	3,284
9	Novel oral anticoagulant*.mp.	2,624
10	Non-vitamin K oral anticoagulant*.mp.	724
11	Non-vitamin K antagonist*.mp.	2,174
12	Direct oral anticoagulant*.mp.	8,411
13	Exp Factor XA inhibitor /	97,313
14	Oral anticoagulant*.tw.	28,113
15	DOAC*.tw.	6,548
16	NOAC*.tw.	5,731
17	OAC*	10,810
18	Rivaroxaban.tw.	12,957
19	Xarelto.tw.	1,353
20	Apixaban.tw.	8,875
21	Eliquis.tw.	769
22	Edoxaban.tw.	3,060
23	Lixiana.tw.	135
24	Dabigatran.tw.	10,683
25	Pradax*.tw.	1,205
26	Prazax*.tw.	15
27	IIa inhibitor*.tw.	213
28	thrombin inhibitor*.tw.	6,853
29	Xa inhibitor*.tw.	4,351
30	10a inhibitor*.tw.	101

31	direct coagulation.tw.	39
32	antithrombin*.tw.	21,780
33	anti-thrombin*.tw.	1,446
34	**8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33**	**148,867**
35	Vitamin-K antagonist*.mp.	12,519
36	VKA.tw.	4,881
37	Phenprocoumon.tw.	1,394
38	Phenprocumon.tw.	10
39	Acenocoumarol.tw.	1,590
40	Acenocumarol.tw.	350
41	Warfarin.tw.	43,073
42	**35 or 36 or 37 or 38 or 39 or 40 or 41**	**54,983**
43	English.lg.	32,606,892
44	French.lg.	724,534
45	German.lg.	926,407
46	Italian.lg.	240,742
47	**43 or 44 or 45 or 46**	**34,402,666**
48	exp Animals/	28,340,064
49	exp Humans/	23,418,359
50	**48 and 49**	**23,418,359**
51	**48 not 50**	**4,921,705**
52	Editorial.pt.	720,877
53	Letter.pt.	1,216,780
54	**52 or 53**	**7,071,048**
55	**(7 and 34 and 42 and 47) not 51 not 54**	**11,843**

Table 61 Search strategy – Cochrane Library [29 March 2022]

No.	Query	Results
1	Atrial fibrillation:kw	10,783
2	Auricular fibrillation:kw	56
3	Atrium fibrillation:kw	2,457
4	non-valvular:kw	10
5	nonvalvular:kw	9
6	NVAF:ti,ab	249
7	**#1 OR #2 OR #3 OR #4 OR #5 OR #6**	**11,088**
8	New oral anticoagulant*:kw	377
9	Novel oral anticoagulant*:kw	147
10	Non-vitamin K oral anticoagulant*:kw	97
11	Non-vitamin K antagonist*:kw	6
12	Direct oral anticoagulant*:kw	460
13	Factor XA inhibitor MeSH	758
14	Oral anticoagulant*:ti,ab	2,916
15	DOAC*:ti,ab	397
16	NOAC*:ti,ab	412
17	OAC*:ti,ab	589
18	Rivaroxaban:ti,ab	1,850
19	Xarelto:ti,ab	93
20	Apixaban:ti,ab	1,011
21	Eliquis:ti,ab	39
22	Edoxaban:ti,ab	596
23	Lixiana:ti,ab	20
24	Dabigatran:ti,ab	1,006
25	Pradax*:ti,ab	51
26	Prazax*:ti,ab	0
27	IIa inhibitor*:ti,ab	481
28	thrombin inhibitor*:ti,ab	1,280
29	Xa inhibitor*:ti,ab	812
30	10a inhibitor*:ti,ab	189

31	direct coagulation:ti,ab	464
32	antithrombin*:ti,ab	1,749
33	anti-thrombin*:ti,ab	109
34	**#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR # 33**	**136,224**
35	Vitamin-K antagonist*:kw	183
36	VKA:ti,ab	516
37	Phenprocoumon:ti,ab	199
38	Phenprocumon:ti,ab	1
39	Acenocoumarol:ti,ab	196
40	Acenocumarol:ti,ab	26
41	Warfarin:ti,ab	4,590
42	**#35 OR #37 OR #38 OR #39 OR #40 OR #41**	**5,275**
43	**#7 AND #34 AND #42**	**1,092**
Filtered		
44	**#43 in Cochrane Reviews**	**9**
45	**#43 in Cochrane Protocols**	**0**
46	**#43 in Trials**	**1,083**
47	**#43 in Editorials**	**0**
48	**#43 in Special Collections**	**0**
49	**#43 in Clinical Answers**	**0**

Table 62 Search strategy -- EconLit (EBSCO) [29 March 2022]

No.	Query	Results
1	atrial fibrillation	21
2	New oral anticoagulant*	1
3	Novel oral anticoagulant*	0
4	Novel oral anticoagulant*	2
5	Non-vitamin K oral anticoagulant*	0
6	Non-vitamin K oral anticoagulant*	4
7	Non-vitamin K antagonist*	0
8	Non-vitamin K antagonist*	7
9	Direct oral anticoagulant*	2
10	Oral anticoagulant*	3
11	DOAC*	2
12	NOAC*	20
13	OAC*	9
14	Rivaroxaban	1
15	Xarelto	0
16	Apixaban	1
17	Eliquis	0
18	Edoxaban	0
19	Lixiana	0
20	Dabigatran	1
21	Pradax*	0
22	Prazax*	0
23	IIa inhibitor*	0
24	IIa inhibitor*	0
25	thrombin inhibitor*	0
26	Xa inhibitor*	0
27	Xa inhibitor*	0
28	10a inhibitor*	21
29	direct coagulation	1
30	antithrombin*	0

31	anti-thrombin*	0
32	**2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31**	**107**
33	**1 AND 32**	**4**

Table 63 Search strategy – INAHTA database [29 March 2022]

No.	Query	Date
1	((Acenocoumarol) OR (Phenprocoumon)) AND ((anti-thrombin*) OR (antithrombin*) OR (direct coagulation) OR (10a inhibitor*) OR (Xa inhibitor*) OR (thrombin inhibitor*) OR (IIa inhibitor*) OR (Prazax*) OR (Pradax*) OR (Dabigatran) OR (Lixiana) OR (Edoxaban) OR (Eliquis) OR (Apixaban) OR (Xarelto) OR (Rivaroxaban) OR (OAC*) OR (NOAC*) OR (DOAC*) OR (Oral anticoagulant*) OR (Direct oral anticoagulant*) OR (Non-vitamin-K antagonist*) OR (Non-vitamin K antagonist*) OR (Non-vitamin K oral anticoagulant*) OR (Novel oral anticoagulant*) OR (New oral anticoagulant*)) AND (Atrial fibrillation)	0

Abbreviations
INAHTA: International network of agencies for health technology assessment

15 Appendix B: Data tables for clinical safety and effectiveness

15.1 Data tables: All-cause mortality

Table 64 All-cause mortality outcomes reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)
ARISTOTLE-J, 2011 [76]	X	3	Apixaban 2.5	72	0	NE
			Apixaban 5	71	0	NE
			Warfarin (INR 2-3)	75	0	Reference
ARISTOTLE, 2011 [75]	X	22	Apixaban 5	9,120	603	0.90 (0.81, 1.00)
			Warfarin (INR 2-3)	9,081	669	Reference
RE-LY, 2009 [81,82]	X	24	Dabigatran 110	6,015	446	0.92 (0.81 to 1.04)
			Dabigatran 150	6,076	438	0.89 (0.79 to 1.01)
			Warfarin (INR 2-3)	6,022	487	Reference
ENGAGE AF, 2013 [78]	+	34	Edoxaban 30	7,034	737	0.88 (0.80 to 0.96)
			Edoxaban 60	7,035	773	0.92 (0.84 to 1.01)
			Warfarin (INR 2-3)	7,036	839	Reference
Weitz et al 2010 [84]	X	3	Edoxaban 30	235	2	1.06 (0.15 to 7.49)
			Edoxaban 60	234	0	0.21 (0.01 to 4.43)
			Warfarin (INR 2-3)	250	2	Reference
Yamashita et al 2012 [85]	X	3	Edoxaban 30	130	0	0.33 (0.01 to 8.05)
			Edoxaban 60	130	1	0.99 (0.06 to 15.70)
			Warfarin (INR 2-3)	129	1	Reference
J-ROCKET AF 2012 [79]	X	30	Rivaroxaban 15	637	7	1.40 (0.45 to 4.39)
			Warfarin (INR 2-3)	637	5	Reference
ROCKET AF 2011 [83]	+	23	Rivaroxaban 20	7,081	582	0.92 (0.83 to 1.03)
			Warfarin (INR 2-3)	7,090	632	Reference

Abbreviations:

CI: confidence interval**; INR:** international normalised ratio**; mg:** milligrams; **mo:** month; **NE:** not estimable; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

+ = low risk; **x** = high risk; **–** = some concerns; **?** = no information.

Table 65 All-cause mortality outcomes reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)	HR (95% CI)
Rodriguez-Bernal et al 2021 [91]	X	10	Apixaban NR	2,259	166	0.53 (0.45 to 0.61)	0.93 (0.79 to 1.09)
		25	Dabigatran NR	32,476	4,539	0.90 (0.82 to 0.99)	0.91 (0.79 to 1.04)
		18	Rivaroxaban NR	3,445	412	0.86 (0.78 to 0.94)	1.02 (0.92 to 1.13)
		22	Acenocoumarol	32,476	4,539	Reference	Reference
Ujeyl et al 2018 [92]	X	12	Apixaban 2.5/5	4,894	NR	NR	1.14 (0.97 to 34)
			Dabigatran 110/150	23,654	NR		1.04 (0.95 to 1.14)
			Rivaroxaban 12/20	59,449	NR		1.17 (1.11 to 1.23)
			Phenprocoumon	118,648	NR		Reference
Warketin et al 2022 [93]	X	12	Apixaban 5	10,997	NR	NR	1.63 (1.50 to 1.77)
			Dabigatran 150	1,914	NR		1.12 (0.94 to 1.33)
			Edoxaban 60	2,255	NR		1.40 (1.22 to 1.61)
			Rivaroxaban 20	6,558	NR		1.45 (1.32 to 1.59)
			Phenprocoumon	20,179	NR		Reference
Korenstra et al 2016 [90]	X	25	Dabigatran 110/150	383	10	0.91 (0.39 to 2.12)	NR
		22	Acenocoumarol	383	11	Reference	
Hohnloser et al 2018 [96]	X	8	Apixaban 2.5/5	10,117	804	1.19 (1.09 to 1.29)	1.05 (0.94 to 1.17)
		9	Dabigatran 110/150	5,122	253	0.74 (0.65 to 0.84)	0.96 (0.80 to 1.15)
		9	Rivaroxaban 15/20	22,143	1,509	1.02 (0.79 to 1.11)	1.12 (1.04 to 1.21)
		12	Phenprocoumon	23,823	1,595	Reference	Reference

Abbreviations:

CI: confidence interval; **HR**: Hazard ratio; **NR:** not reported; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

Trials did not report results per intervention doses.

+ = low risk; **−** = moderate risk; **x** = serious risk; **xx** = critical risk; **?** = no information.

15.2 Data tables: Cardiovascular-related mortality

Table 66 Cardiovascular-related mortality outcomes reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)
ARISTOTLE, 2010 [75]	X	22	Apixaban 5.0	9,120	308	
			Warfarin	9,081	344	
RE-LY, 2009 [81,82]	X	24	Dabigatran 110	6,015	289	0.91 (0.78 to 1.07)
			Dabigatran 150	6,076	274	0.86 (0.77 to 1.00)
			Warfarin	6,022	317	Reference
ENGAGE AF-TIMI 48, 2013 [78]	+	37	Edoxaban 30	7,034	527	0.86 (0.77 to 0.96)
			Edoxaban 60	7,035	530	0.86 (0.78 to 0.97)
			Warfarin	7,036	611	Reference
ROCKET AF, 2011 [83]	+	23	Rivaroxaban 20	7,018	170	0.88 (0.72 to 1.08)
			Warfarin	7,061	193	Reference

Abbreviations:

CI: confidence interval**; INR:** international normalised ratio**; mg:** milligrams; **mo:** month; **NE:** not estimable; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

Warfarin was the VKA used in all included trials.

+ = low risk; **x** = high risk; **–** = some concerns; **?** = no information.

Table 67 Cardiovascular-related mortality outcomes reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	events	RR (95% CI)	HR (95% CI)
Korenstra et al 2016 [90]	X	25	Dabigatran 110/150	383	0		NR
		22	Acenocoumarol	383	4		
Ujeyl et al 2018 [92]	X	12	Apixaban 2.5/5	4,894	NR	NR	1.14 (0.96 to 1.35)
			Dabigatran 110/150	23,654	NR		1.06 (0.97 to 1.16)
			Rivaroxaban 12/20	59,449	NR		1.18 (1.12 to 1.24)
			Phenprocoumon	118,648	NR		Reference

Abbreviations:

CI: confidence interval; **HR**: Hazard ratio; **NR:** not reported; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

Trials did not report results per intervention doses.

+ = low risk; **–** = moderate risk; **x** = serious risk; **xx** = critical risk; **?** = no information.

15.3 Data tables: Major/life-threatening bleeding

Table 68 Major/life-threatening bleeding outcomes reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)
ARISTOTLE-J, 2011 [76]	✗	3	Apixaban 2.5	72	0	0.35 (0.01 to 8.38)
			Apixaban 5	71	0	0.35 (0.01 to 8.50)
			Warfarin (INR 2-3)	75	1	Reference
ARISTOTLE, 2011 [75]	✗	22	Apixaban 5	9,088	327	
			Warfarin (INR 2-3)	9,052	462	
RE-LY, 2009 [81,82]	✗	24	Dabigatran 110	6,015	342	0.81 (0.71 to 0.93)
			Dabigatran 150	6,076	399	0.94 (0.82 to 1.07)
			Warfarin (INR 2-3)	6,022	421	Reference
PETRO, 2009 [80]	✗	3	Dabigatran 150	100	0	NE
			Warfarin (INR 2-3)	70	0	Reference
ENGAGE AF, 2013 [78]	+	34	Edoxaban 30	7,002	254	0.49 (0.42 to 0.56)
			Edoxaban 60	7,012	418	0.80 (0.71 to 0.90)
			Warfarin (INR 2-3)	7,012	524	Reference
Weitz et al 2010 [84]	✗	3	Edoxaban 30	235	0	0.35 (0.01 to 8.66)
			Edoxaban 60	234	1	1.06 (0.07 to 16.91)
			Warfarin (INR 2-3)	250	1	Reference
Yamashita et al 2012 [85]	✗	3	Edoxaban 30	130	0	NE
			Edoxaban 60	130	2	4.81 (0.23 to 99.19)
			Warfarin (INR 2-3)	125	0	Reference
ROCKET AF, 2011 [83]	+	23	Rivaroxaban 20	7,111	395	1.03 (0.89 to 1.18)
			Warfarin (INR 2-3)	7,125	386	Reference

Abbreviations:

CI: confidence interval**; INR:** international normalised ratio**; mg:** milligrams; **mo:** month; **NE:** not estimable; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

+ = low risk; **x** = high risk. **−** = some concerns; **?** = no information.

Table 69 Major/life threating bleeding outcomes reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)	HR (95% CI)
Ramagopalan et al 2019 [95]	✗	12	Apixaban 5/10	2,160	52		0.51 (0.37 to 0.70)
			Acenocoumarol	2,160	100		Reference
Rodriguez-Bernal et al 2021 [91]	✗	10	Apixaban NR	2,259	5	0.28 (0.12 to 0.68)	0.42 (0.17 to 1.03)
		25	Dabigatran NR	32,476	22	0.83 (0.53 to 1.27)	0.93 (0.60 to 1.45)
		18	Rivaroxaban NR	3,445	18	0.66 (0.41 to 1.07)	0.80 (0.49 to 1.29)

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)	HR (95% CI)
		22	Acenocoumarol	32,476	256	Reference	Reference
Ujeyl et al 2018 [92]	X	12	Apixaban 2.5/5	4,894	NR	NR	0.65 (0.50 to 0.85)
			Dabigatran 110/150	23,654	NR		0.87 (0.77 to 0.98)
			Rivaroxaban 12/20	59,449	NR		1.04 (0.97 to 1.12)
			Phenprocoumon	118,684	NR		Reference
Korenstra et al 2016 [90]	X	25	Dabigatran 110/150	383	10		NR
		22	Acenocoumarol	383	28		
RE-SONANCE, 2020 [88]	X X	12	Dabigatran 110/150	3,179	14		NR
			Acenocoumarol, Phenprocoumon, Warfarin	2,186	7		
van den Ham et al 2021 [87]	X	15	Apixaban10	7,727	NR	NR	0.76 (0.69 to 0.84)
			Dabigatran 150	24,765	NR		0.85 (0.75 to 0.96)
			Rivaroxaban 20	63,327	NR		1.11 (1.06 to 1.16)
			Acenocoumarol, Phenprocoumon, Fluindione, Warfarin	381,145	NR		Reference
Hohnloser et al 2018 [96]	X	8	Apixaban 2.5/5	10,117	167	0.57 (0.48 to 0.67)	0.58 (0.48 to 0.70)
		9	Dabigatran 110/150	5,122	80	0.54 (0.43 to 0.68)	0.51 (0.39 to 0.67)
		9	Rivaroxaban 15/20	22,143	568	0.88 (0.79 to 0.99)	1.09 (0.96 to 1.24)
		12	Phenprocoumon	23,823	692	Reference	Reference

Abbreviations:

CI: confidence interval; **HR**: Hazard ratio; **NR:** not reported; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

Trials did not report results per intervention doses.

+ = low risk; **−** = moderate risk; **x** = serious risk; **xx** = critical risk; **?** = no information.

15.4 Data tables: Intracranial bleeding

Table 70 Intracranial bleeding outcomes reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)
ARISTOTLE, 2011 [75]	✗	22	Apixaban 5	9,088	52	0.42 (0.31 to 0.59)
			Warfarin (INR 2-3)	9,052	122	Reference
RE-LY, 2009 [81,82]	✗	24	Dabigatran 110	6,015	27	0.31 (0.20 to 0.48)
			Dabigatran 150	6,076	36	0.41 (0.28 to 0.60)
			Warfarin (INR 2-3)	6,022	87	Reference
ENGAGE AF, 2013 [78]	+	34	Edoxaban 30	7,002	41	0.31 (0.22 to 0.44)
			Edoxaban 60	7,120	61	0.46 (0.34 to 0.62)
			Warfarin (INR 2-3)	7,012	132	Reference
J-ROCKET AF, 2012 [79]	✗	30	Rivaroxaban 15	639	5	0.50 (0.17 to 1.45)
			Warfarin (INR 2-3)	639	10	Reference
ROCKET AF, 2011 [83]	+	23	Rivaroxaban 20	7,111	55	0.66 (0.47 to 0.92)
			Warfarin (INR 2-3)	7,125	84	Reference

Abbreviations:

CI: confidence interval**; INR:** international normalised ratio**; mg:** milligrams; **mo:** month; **NE:** not estimable; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

+ = low risk; **x** = high risk. **−** = some concerns; **?** = no information.

Table 71 Intracranial bleeding outcomes reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)	HR (95% CI)
Ramagopalan et al 2019 [95]	✗	12	Apixaban 5/10	2,160	8	0.73 (0.29 to 1.80)	NR
			Acenocoumarol	2,160	11	Reference	
Rodriguez-Bernal et al 2021 [91]	✗	10	Apixaban NR	2,259	10	0.33 (0.18 to 0.62)	0.44 (0.18 to 1.07)
		25	Dabigatran NR	32,476	16	0.49 (0.32 to 0.75)	0.91 (0.59 to 1.42)
		18	Rivaroxaban NR	3,445	21	0.46 (0.30 to 0.71)	0.82 (0.50 to 1.32)
		22	Acenocoumarol	32,476	430	Reference	Reference
Ujeyl et al 2018 [92]	✗	12	Apixaban 2.5/5	4,894	NR	NR	0.79 (0.36 to 1.73)
			Dabigatran 110/150	23,654	NR		0.40 (0.27 to 0.59)
			Rivaroxaban 12/20	59,449	NR		0.57 (0.47 to 0.69)
			Phenprocoumon	118,648	NR		Reference
van den Ham		15	Apixaban 10	7,727	NR	NR	0.61 (0.51 to

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)	HR (95% CI)
et al 2021 [87]	✗						0.73)
			Dabigatran 150	24,765	NR		0.48 (0.36 to 0.64)
			Rivaroxaban 20	63,327	NR		0.75 (0.61 to 0.92)
			Acenocoumarol, Phenprocoumon, Fluindione, Warfarin	381,145	NR		Reference
Korenstra et al 2016 [90]	✗	25	Dabigatran 110/150	383	0	5.96 (3.74 to 9.51]	NR
		22	Acenocoumarol	383	2	Reference	
Hohnloser et al 2018 [96]	✗	8	Apixaban 2.5/5	10,117	35	0.47 (0.33 to 0.68)	0.39 (0.25 to 0.61)
		9	Dabigatran 110/150	5,122	20	0.53 (0.34 to 0.84)	0.41 (0.24 to 0.70)
		9	Rivaroxaban 15/20	22,143	106	0.65 (0.51 to 0.83)	0.74 (0.57 to 0.96)
		12	Phenprocoumon	23,823	175	Reference	Reference

Abbreviations:

CI: confidence interval; **HR**: hazard ratio; **NR:** not reported; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

Trials did not report results per intervention doses.

+ = low risk; **−** = moderate risk; **x** = serious risk; **xx** = critical risk; **?** = no information.

15.5 Data tables: Gastrointestinal bleeding

Table 72 Gastrointestinal bleeding outcomes reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)
ARISTOTLE, 2011 [75]	✗	22	Apixaban 5	9,088	105	0.88 (0.68 to 1.14)
			Warfarin (INR 2-3)	9,052	119	Reference
ENGAGE AF, 2013 [78]	+	34	Edoxaban 30	7,002	129	0.68 (0.55 to 0.85)
			Edoxaban 60	7,012	232	1.22 (1.01 to 1.47)
			Warfarin (INR 2-3)	7,012	190	Reference
J-ROCKET AF, 2012 [79]	✗	30	Rivaroxaban 15	639	6	0.50 (0.19 to 1.32)
			Warfarin (INR 2-3)	639	12	Reference
RE-LY, 2009 [81,82]	✗	24	Dabigatran 110	6,015	137	1.09 (0.86 to 1.38)
			Dabigatran 150	6,076	188	1.48 (1.18 to 1.85)
			Warfarin (INR 2-3)	6,022	126	Reference
ROCKET AF, 2011 [83]	+	23	Rivaroxaban 20	7,111	224	1.46 (1.19 to 1.78)
			Warfarin (INR 2-3)	7,125	154	Reference

Abbreviations:

CI: confidence interval**; INR:** international normalised ratio**; mg:** milligrams; **mo:** month; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

+ = low risk; **x** = high risk;.**−** = some concerns; **?** = no information.

Table 73 Gastrointestinal bleeding outcomes reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose	Sample size	Events	RR (95% CI)	HR (95% CI)
Ramagopalan et al 2019 [95]	X	12	Apixaban 5/10	2,160	37		NR
			Acenocoumarol	2,160	69		
Rodriguez-Bernal et al 2021 [91]	X	10	Apixaban NR	2,259	12	0.36 (0.20 to 0.63)	0.57 (0.32 to 1.01)
		25	Dabigatran NR	32,476	59	1.15 (0.88 to 1.51)	1.22 (0.93 to 1.60)
		18	Rivaroxaban NR	3,445	39	0.76 (0.55 to 1.06)	0.93 (0.67 to 1.29)
		22	Acenocoumarol	32,476	482	Reference	Reference
Ujeyl et al 2018 [92]	X	12	Apixaban 2.5/5	4,894	NR	NR	0.70 (0.48 to 1.02)
			Dabigatran 110/150	23,654	NR		1.21 (1.03 to 1.42)
			Rivaroxaban 12/20	59,449	NR		1.28 (1.17 to 1.40)
			Phenprocoumon	118,648	NR		Reference
van den Ham et al 2021 [87]	X	15	Apixaban 10	7,727	NR	NR	0.77 (0.67 to 0.88)
			Dabigatran 150	24,765	NR		1.16 (1.05 to 1.28)
			Rivaroxaban 20	63,327	NR		1.28 (1.18 to 1.39)
			Acenocoumarol, Phenprocoumon, Fluindione, Warfarin	381,145	NR		Reference
Korenstra et al 2016 [90]	X	25	Dabigatran 110/150	383	1	0.20 (0.02 to 1.70)	NR
		22	Acenocoumarol	383	5	Reference	
Hohnloser et al 2018 [96]	X	8	Apixaban 2.5/5	10,117	213	0.08 (0.07 to 0.09)	0.71 (0.59 to 0.85)
		9	Dabigatran 110/150	5,122	123	0.78 (0.65 to 0.95)	0.93 (0.73 to 1.18)
		9	Rivaroxaban 15/20	22,143	759	1.12 (1.01 to 1.24)	1.35 (1.20 to 1.52)
		12	Phenprocoumon	23,823	730	Reference	Reference

Abbreviations:

CI: confidence interval; **HR**: Hazard ratio; **NR:** not reported; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

Trials did not report results per intervention doses.

+ = low risk; **−** = moderate risk; **x** = serious risk; **xx** = critical risk; **?** = no information.

15.6 Data tables: Clinically-relevant bleeding

Table 74 Clinically-relevant bleeding outcomes reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)
ARISTOTLE-J 2011 [75]	✗	3	Apixaban 2.5	72	1	0.35 (0.04 to 3.26)
			Apixaban 5	71	1	0.35 (0.04 to 3.31)
			Warfarin (INR 2-3)	75	3	Reference
PETRO, 2009 [80]	✗	3	Dabigatran 150	100	9	
			Warfarin (INR 2-3)	70	4	
ENGAGE AF, 2013 [78]	+	34	Edoxaban 30	7,002	969	0.70 (0.64 to 0.75)
			Edoxaban 60	7,012	1,214	0.87 (0.81 to 0.93)
			Warfarin (INR 2-3)	7,012	1,396	Reference
Weitz et al 2010 [84]	✗	3	Edoxaban 30	235	7	1.06 (0.38 to 2.99)
			Edoxaban 60	234	8	1.22 (0.45 to 3.31)
			Warfarin (INR 2-3)	250	7	Reference
ROCKET AF, 2011 [83]	+	23	Rivaroxaban 20	7,111	1,185	1.06 (0.99 to 1.15)
			Warfarin (INR 2-3)	7,125	1,115	Reference

Abbreviations:

CI: confidence interval**; INR:** international normalised ratio**; mg:** milligrams; **mo:** month; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

+ = low risk; **x** = high risk.; **−** = some concerns; **?** = no information.

Table 75 Clinically-relevant bleeding outcomes reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	events	RR (95% CI)	HR (95% CI)
Paschke et al 2020 [89]	✗ ✗	15	Apixaban 2.5/5	127,610	NR	NR	0.71 (0.70 to 0.72)
		15	Dabigatran 75-110	53,233	NR		0.85 (0.83 to 0.87)
		15	Edoxaban 15-60	13,266	NR		0.74 (0.68 to 0.81)
		15	Rivaroxaban 2.5-20	229,926	NR		1.03 (1.01 to 1.05)
		20	Phenprocoumon	347,297	NR		Reference
Warketin et al 2022 [93]	✗	12	Apixaban 5	10,997	NR	NR	0.75 (0.65 to 0.87)
			Dabigatran 150	1,914	NR		0.86 (0.64 to 1.16)
			Edoxaban 60	2,255	NR		0.95 (0.75 to 1.20)
			Rivaroxaban 20	6,558	NR		1.11 (0.96 to 1.28)
			Phenprocoumon	20,179	NR		Reference
Hohnloser et al 2018 [96]	✗	8	Apixaban 2.5/5	10,117	822	0.75 (0.70 to 0.81)	0.78 (0.71 to 0.86)
		9	Dabigatran 110/150	5,122	393	0.71 (0.64 to 0.79)	0.82 (0.71 to 0.95)
		9	Rivaroxaban 15/20	22,143	2,276	0.95 (0.90 to 1.00)	1.12 (1.05 to 1.19)
		12	Phenprocoumon	23,823	2,573	Reference	Reference

Abbreviations:

CI: confidence interval; **HR**: Hazard ratio; **n:** sample size; **NR:** not reported; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

Trials did not report results per intervention doses.

+ = low risk; **−** = moderate risk; **x** = serious risk; **xx** = critical risk; **?** = no information.

15.7 Data tables: All stroke and systemic embolic events

Table 76 All stroke and systemic embolic event outcomes reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)
ARISTOTLE-J, 2011 [76]	x	3	Apixaban 2.5	72	0	0.11 (0.01 to 2.08)
			Apixaban 5	71	0	0.12 (0.01 to 2.14)
			Warfarin (INR 2-3)	75	4	Reference
ARISTOTLE, 2011 [75]	x	22	Apixaban 5	9,120	212	0.80 (0.67 to 0.95)
			Warfarin (INR 2-3)	9,081	265	Reference
RE-LY, 2009 [81,82]	x	24	Dabigatran 110	6,015	183	0.91 (0.74 to 1.10)
			Dabigatran 150	6,076	134	0.91 (0.74 to 1.10)
			Warfarin (INR 2-3)	6,022	202	Reference
PETRO, 2009 [80]	x	3	Dabigatran 150	100	0	NE
			Warfarin (INR 2-3)	70	0	
ENGAGE AF, 2013 [78]	+	34	Edoxaban 30	7,034	383	1.14 (0.99 to 1.31)
			Edoxaban 60	7,035	296	0.88 (0.75 to 1.02)
			Warfarin (INR 2-3)	7,036	337	Reference
Weitz, 2010 [84]	x	3	Edoxaban 30	235	1	0.27 (0.03 to 2.36)
			Edoxaban 60	234	1	0.27 (0.03 to 2.37)
			Warfarin (INR 2-3)	250	4	Reference
Yamashita, 2012 [85]	x	3	Edoxaban 30	130	0	NE
			Edoxaban 60	130	0	NE
			Warfarin (INR 2-3)	129	0	Reference
J-ROCKET AF, 2012 [79]	x	30	Rivaroxaban 15	637	11	0.50 (0.24 to 1.02)
			Warfarin (INR 2-3)	637	22	Reference
ROCKET AF, 2011 [83]	+	23	Rivaroxaban 20	7,081	269	0.88 (0.75 to 1.03)
			Warfarin (INR 2-3)	7,090	306	Reference

Abbreviations:

CI: confidence interval**; INR:** international normalised ratio**; mg:** milligrams; **mo:** month; **NE:** not estimable; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

+ = low risk; **x** = high risk;.**−** = some concerns; **?** = no information.

Table 77 Systemic embolic events outcomes reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)	HR (95% CI)
Korenstra et al 2016 [90]	X	25	Dabigatran 110/150	383	44	0.55 (0.38 to 0.79)	0.72 (0.27 to 1.91)
		22	Acenocoumarol	383	80	Reference	Reference
Ramagopalan et al 2019 [95]	X	12	Apixaban 5/10	2,160	4	0.57 (0.17 to 1.94)	0.54 (0.38 to 0.77)
			Acenocoumarol	2,160	7	Reference	Reference
Paschke et al 2020 [89]	X X	15	Apixaban 2.5/5	132,869	NR	NR	0.75 (0.67 to 0.84)
		15	Dabigatran 75-110	52,796	NR		0.93 (0.79 to 1.09)
		15	Edoxaban 15-60	14,556	NR		0.29 (0.17 to 0.49)
		15	Rivaroxaban 2.5-20	228,513	NR		0.83 (0.77 to 0.89)
		20	Phenprocoumon	347,297	NR		Reference
Warketin et al 2022 [93]	X	12	Apixaban 5	10,997	NR	NR	1.42 (1.21 to 1.67)
			Dabigatran 150	1,914	NR		1.04 (0.77 to 1.40)
			Edoxaban 60	2,255	NR		1.25 (0.95 to 1.64)
			Rivaroxaban 20	6,558	NR		1.20 (1.00 to 1.44)
			Phenprocoumon	20,179	NR		Reference
Hohnloser et al 2018 [96]	X	8	Apixaban 2.5/5	10,117	226	0.89 (0.77 to 1.04)	0.77 (0.64 to 0.93)
		9	Dabigatran 110/150	5,122	104	0.81 (0.66 to 1.00)	0.74 (0.57 to 0.96)
		9	Rivaroxaban 15/20	22,143	456	0.82 (0.73 to 0.93)	0.89 (0.77 to 1.03)
		12	Phenprocoumon	23,823	597	Reference	Reference

Abbreviations:

CI: confidence interval; **HR**: Hazard ratio; **NR:** not reported; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

Trials did not report results per intervention doses.

+ = low risk; **−** = moderate risk; **x** = serious risk; **xx** = critical risk; **?** = no information.

15.8 Data tables: Ischaemic stroke

Table 78 Ischaemic stroke outcomes reported by RCTs

Trial name	RoB	Timepoint of assessment	Intervention and dose	Sample size	Events	RR (95% CI)
ARISTOTLE, 2011 [75]	X	22	Apixaban 5	9,120	162	0.92 (0.75 to 1.14)
			Warfarin (INR 2-3)	9,081	175	Reference
RE-LY, 2009 [81,82]	X	24	Dabigatran 110	6,015	159	1.12 (0.90 to 1.40)
			Dabigatran 150	6,076	111	0.77 (0.61 to 0.99)
			Warfarin (INR 2-3)	6,022	142	Reference
ENGAGE AF,		34	Edoxaban 30	7,034	333	1.42 (1.20 to 1.67)

Trial name	RoB	Timepoint of assessment	Intervention and dose	Sample size	Events	RR (95% CI)
2013 [78]	+		Edoxaban 60	7,035	236	1.00 (0.84 to 1.20)
			Warfarin (INR 2-3)	7,036	235	Reference
J-ROCKET AF, 2012 [79]	x	30	Rivaroxaban 15	639	7	0.41 (0.17 to 0.99)
			Warfarin (INR 2-3)	639	17	Reference
ROCKET AF, 2011 [83]	+	23	Rivaroxaban 20	7,111	149	0.93 (0.74 to 1.16)
			Warfarin (INR 2-3)	7,125	161	Reference

Abbreviations:

CI: confidence interval**; INR:** international normalised ratio**; mg:** milligrams; **mo:** month; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

+ = low risk; **x** = high risk;**−** = some concerns; **?** = no information.

Table 79 Ischaemic stroke events outcomes reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)	HR (95% CI)
Ramagopalan et al 2019 [95]	x	12	Apixaban 5/10	2,160	30	0.50 (0.32 to 0.77)	NR
			Acenocoumarol	2,160	60	Reference	
Rodriguez-Bernal et al 2021 [91]	x	10	Apixaban NR	2,259	35	0.80 (0.57 to 1.12)	1.32 (0.94 to 1.87)
		25	Dabigatran NR	32,476	75	1.15 (0.91 to 1.46)	1.02 (0.98 to 1.07)
		18	Rivaroxaban NR	3,445	59	0.89 (0.68 to 1.16)	1.03 (0.79 to 1.35)
		22	Acenocoumarol	32,476	627	Reference	Reference
Paschke et al 2020 [89]	x x	15	Apixaban 2.5/5	132,869	NR	NR	1.52 (1.46 to 1.58)
		15	Dabigatran75-110	52,796	NR		1.93 (1.82 to 2.05)
		20	Phenprocoumon	347,297	NR		Reference
Ujeyl et al 2018 [92]	x		Apixaban 2.5/5	4,894	NR	NR	1.84 (1.20 to 2.82)
			Dabigatran 110/150	1914	NR		1.14 (0.97 to 1.34)
			Rivaroxaban 12/20	59449	NR		1.05 (0.94 to 1.17)
			Phenprocoumon	118,648	NR		Reference
Warketin et al 2022 [93]	x	12	Dabigatran 150	1,914	NR	NR	1.14 (0.97 to 1.34)
			Phenprocoumon	20,179	NR		
Korenstra et al 2016 [90]	x	25	Dabigatran 110/150	383	2	0.67 (0.11 to 3.97)	NR
		22	Acenocoumarol	383	3		
van den Ham et al 2021 [87]	x	15	Apixaban 10	7,727	NR	NR	0.94 (0.75 to 1.18)
			Dabigatran 150	24,765	NR		0.96 (0.80 to

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)	HR (95% CI)
							1.15)
			Rivaroxaban 20	63,327	NR		0.99 (0.85 to 1.15)
			Acenocoumarol, Phenprocoumon, Fluindione, Warfarin	381,145	NR		Reference
Hohnloser et al 2018 [96]	✗	8	Apixaban 2.5/5	10,117	165	0.97 (0.81 to 1.17)	0.82 (0.66 to 1.02)
		9	Dabigatran 110/150	5,122	82	0.96 (0.76 to 1.21)	0.86 (0.64 to 1.16)
		9	Rivaroxaban 15/20	22,143	322	0.87 (0.75 to 1.00)	0.91 (0.77 to 1.08)
		12	Phenprocoumon	23,823	399	Reference	Reference

Abbreviations:

CI: confidence interval; **HR**: Hazard ratio; **NR:** not reported; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

Trials did not report results per intervention doses.

+ = low risk; **−** = moderate risk; **x** = serious risk; **xx** = critical risk; **?** = no information.

15.9 Data tables: Haemorrhagic stroke

Table 80 Haemorrhagic stroke outcomes reported by RCTs

Trial name	RoB	Timepoint of assessment	Intervention and dose	Sample size	Events	RR (95% CI)
ARISTOTLE, 2011 [75]	✗	22	Apixaban 5	9,120	40	0.51 (0.35 to 0.75)
			Warfarin (INR 2-3)	9,081	78	Reference
RE-LY, 2009 [81,82]	✗	24	Dabigatran 110	6,015	14	0.31 (0.17 to 0.57)
			Dabigatran 150	6,076	12	0.26 (0.14 to 0.50)
			Warfarin (INR 2-3)	6,022	45	Reference
ENGAGE AF, 2013 [78]	+	34	Edoxaban 30	7,034	30	0.33 (0.22 to 0.50)
			Edoxaban 60	7,035	49	0.54 (0.39 to 0.77)
			Warfarin (INR 2-3)	7,036	90	Reference
J-ROCKET AF, 2012 [79]	✗	30	Rivaroxaban 15	639	3	0.75 (0.17 to 3.34)
			Warfarin (INR 2-3)	639	4	Reference
ROCKET AF, 2011 [83]	+	23	Rivaroxaban 20	7,081	29	0.58 (0.37 to 0.92)
			Warfarin (INR 2-3)	7,090	50	Reference

Abbreviations:

CI: confidence interval**; INR:** international normalised ratio**; mg:** milligrams; **mo:** month; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

+ = low risk; **x** = high risk;**−** = some concerns; **?** = no information.

Table 81 Haemorrhagic stroke outcomes reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)	HR (95% CI)
Hohnloser et al 2018 [96]	⊗	8	Apixaban 2.5/5	10,117	25	0.49 (0.32 to 0.76)	0.39 (0.23 to 0.66)
		9	Dabigatran 110/150	5,122	10	0.39 (0.21 to 0.74)	0.27 (0.14 to 0.52)
		9	Rivaroxaban 15/20	22,143	78	0.71 (0.53 to 0.94)	0.79 (0.58 to 1.08)
		12	Phenprocoumon	23,823	119	Reference	Reference

Abbreviations:

CI: confidence interval; **HR**: Hazard ratio; **NR:** not reported; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

Trials did not report results per intervention doses.

+ = low risk; **−** = moderate risk; **x** = serious risk; **xx** = critical risk; **?** = no information.

15.10 Data tables: Adherence

Table 82 Adherence outcomes reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)
ROCKET AF, 2011 [83]	⊕	23	Rivaroxaban 20	7,111	6,977	
			Warfarin (INR 2-3)	7,125	6,961	

Abbreviations:

CI: confidence interval**; INR:** international normalised ratio**; mg:** milligrams; **mo:** month; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

+ = low risk; **x** = high risk; **−** = some concerns; **?** = no information.

15.11 Data tables: Persistence

Table 83 Persistence outcomes reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)
ARISTOTLE-J, 2011 [76]	✗	3	Apixaban 2.5	74	67	1.03 (0.92 to 1.15)
			Apixaban 5.0	74	69	1.06 (0.96 to 1.18)
			Warfarin (INR 2-3)	74	65	Reference
ARISTOTLE, 2010 [75]	✗	22	Apixaban 5.0	9,194	7,210	1.03 (0.92 to 1.04)
			Warfarin (INR 2-3)	9,155	7,002	Reference
RE-LY, 2009 [81,82]	✗	24	Dabigatran 110	6,015	4,854	0.95 (0.93 to 0.96)
			Dabigatran 150	6,076	4,865	0.94 (0.93 to 0.96)
			Warfarin (INR 2-3)	6,022	5,120	Reference
ENGAGE AF-TIMI 48, 2013 [78]	+	37	Edoxaban 30	7,034	6,250	1.02 (1.00 to 1.03)
			Edoxaban 60	7,035	6,228	1.01 (1.00 to 1.02)
			Warfarin (INR 2-3)	7,036	6,157	Reference
Yamashita et al 2012 [85]	✗	3	Edoxaban 30	135	121	0.96 (0.89 to 1.03)
			Edoxaban 60	132	119	0.97 (0.90 to 1.04)
			Warfarin (INR 2-3)	134	125	Reference
Weitz et al 2010 [84]	✗	3	Edoxaban 30	245	244	0.96 (0.89 to 1.03)
			Edoxaban 60	180	180	0.97 (0.90 to 1.04)
			Warfarin (INR 2-3)	251	250	Reference
J-ROCKET AF, 2012 [79]	✗	23	Rivaroxaban 15	640	637	1.00 (0.99 to 1.01)
			Warfarin (INR 2-3)	640	637	Reference
ROCKET AF, 2011 [83]	+	23	Rivaroxaban 20	7,131	5,440	0.98 (0.96 to 1.00)
			Warfarin (INR 2-3)	7,133	5,549	Reference

Abbreviations:

CI: confidence interval**; INR:** international normalised ratio**; mg:** milligrams; **mo:** month; **RR**: relative risk/ risk ratio; **RoB**: risk of bias.

Notes:

+ = low risk; **x** = high risk;. **−** = some concerns; **?** = no information.

Table 84 Persistence outcomes reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)	HR (95% CI)
Ramagopalan et al 2019 [95]	✗	12	Apixaban 5/10	2,160	1,536	1.17 (1.12 to 1.23)	NR
			Acenocoumarol	2,160	1,309	Reference	
Zielinski et al 2020 [94]	✗	12	Apixaban 2.5/5	13,878	4,996	0.56 (0.55 to 0.58)	NR
			Dabigatran ≤150	29,288	6,443	0.34 (0.33 to 0.35)	
			Rivaroxaban 12/20	34,167	16,742	0.77 (0.75 to 0.78)	
			Acenocoumarol, Phenprocoumon, Warfarin	10,079	6,451	Reference	

Abbreviations:

CI: confidence interval; **HR:** hazard ratio; **NR**: not reported; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

Trials did not report results per intervention doses.

+ = low risk; **−** = moderate risk; **x** = serious risk; **xx** = critical risk; **?** = no information.

15.12 Data tables: Health-related quality of life

Table 85 Health-related quality of life reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Tool/ scale	Intervention and dose (mg)	Sample size	Mean	SD	MD (95% CI)
RE-LY [81,82]	✗	12	EQ-5D-VAS	Dabigatran 110	497	73.4	41.98	-0.50 (-4.95 to 3.95)
				Dabigatran 150	485	72.2	33.62	-1.70 (-5.60 to 2.19)
				Warfarin (INR 2-3)	453	73.9	27.07	Reference

Abbreviation:

CI: confidence interval; **DOAC:** direct-acting oral anticoagulants; **EQ-5D-VAS:** EuroQol 5-dimension with visual analogue scale; **MD:** mean difference; **RoB**: risk of bias; **SD:** standard deviation; **VKA:** vitamin-K antagonist.

Notes:

+ = low risk; **x** = high risk; **−** = some concerns; **?** = no information.

15.13 Data tables: Treatment discontinuation due to adverse events

Table 86 Treatment discontinuation due to adverse events reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)
ARISTOTLE-J, 2011 [76]	✗	3	Apixaban 2.5	72	4	1.04 (0.27 to 4.01)
			Apixaban 5.0	71	4	1.06 (0.27 to 4.06)
			Warfarin (INR 2-3)	75	4	Reference
ARISTOTLE 2010 [75]	✗	22	Apixaban 5.0	9,120	679	0.92 (0.83 to 1.01)
			Warfarin (INR 2-3)	9,081	738	Reference
RE-LY, 2009 [81,82]	✗	24	Dabigatran 110	6,015	355	1.51 (1.29 to 1.78)
			Dabigatran 150	6,076	330	1.39 (1.18 to 1.64)
			Warfarin (INR 2-3)	6,022	235	Reference
PETRO, 2009 [80]	✗	3	Dabigatran 150	169	9	7.94 (0.47 to 134.51)
			Warfarin (INR 2-3)	70	0	Reference
ENGAGE AF-TIMI 48, 2013 [78]	+	37	Edoxaban 30	7,034	1,093	0.94 (0.87 to 1.01)
			Edoxaban 60	7,035	1,204	1.03 (0.96 to 1.11)
			Warfarin (INR 2-3)	7,036	1,168	Reference
ROCKET AF, 2011 [83]	+	23	Rivaroxaban 20	7,131	594	1.19 (1.06 to 1.34)
			Warfarin (INR 2-3)	7,133	498	Reference

Abbreviations:

CI: confidence interval**; INR:** international normalised ratio**; mg:** milligrams; **mo:** month; **RR**: relative risk/ risk ratio; **RoB**: risk of bias.

Notes:

+ = low risk; **x** = high risk;**−** = some concerns; **?** = no information.

Table 87 Treatment discontinuation due to adverse event outcomes reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention and dose (mg)	Sample size	Events	RR (95% CI)	HR (95% CI)
RE-SONANCE, 2020 [88]	✗✗	12	Dabigatran 110/150	3,179	32	5.50 (1.95 to 15.53)	NR
			Acenocoumarol, Warfarin	2,186	4	Reference	
Ujeyl et al 2018 [92]	✗	12	Apixaban 2.5/5	4,894	1,625	1.62 (1.55 to 1.69)	NR
			Dabigatran 110/150	23,654	8,657	1.79 (1.75 to 1.82)	
			Rivaroxaban 12/20	59,449	28,35	1.46 (1.42 to 1.51)	
			Phenprocoumon	87,997	18,039	Reference	

Abbreviations:

CI: confidence interval; **HR:** hazard ratio; **NR**: not reported; **RoB**: risk of bias; **RR**: relative risk/ risk ratio.

Notes:

Trials did not report results per intervention doses.

+ = low risk; **−** = moderate risk; **x** = serious risk; **xx** = critical risk; **?** = no information.

16 Appendix C: GRADE evidence profile tables

Table 88 GRADE evidence profile: all-cause mortality reported in the included RCTs

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban 2.5 mg twice daily	1	randomised trials	very serious[a]	N/A	not serious	N/A	none	0/72 (0.0%)	0/75 (0.0%)	not estimable	not estimable	N/A
Apixaban 5 mg twice daily	2	randomised trials	very serious[a]	not serious	not serious	not serious	none	669/9191 (7.3%)	603/9156 (6.6%)	RR 0.90 (0.81 to 1.00)	7 fewer per 1,000 (from 13 fewer to 0 fewer)	⊕⊕◯◯ Low
Dabigatran 110 mg twice daily	1	randomised trials	serious[e]	not serious	not serious	not serious	none	446/6015 (7.4%)	487/6022 (8.1%)	RR 0.92 (0.81 to 1.04)	6 fewer per 1,000 (from 14 fewer to 3 more)	⊕⊕⊕◯ Moderate
Dabigatran 150 mg twice daily	1	randomised trials	serious[e]	not serious	not serious	not serious	none	438/6076 (7.2%)	487/6022 (8.1%)	RR 0.89 (0.79 to 1.01)	9 fewer per 1,000 (from 17 fewer to 1 more)	⊕⊕⊕◯ Moderate
Edoxaban 30 mg once daily	3	randomised trials	serious[c]	not serious	not serious	not serious	none	739/7399 (10.0%)	842/7415 (11.4%)	RR 0.88 (0.80 to 0.96)	14 fewer per 1,000 (from 23 fewer to 5 fewer)	⊕⊕⊕◯ Moderate
Edoxaban 60 mg once daily	3	randomised trials	serious[a]	not serious	not serious	not serious	none	774/7399 (10.5%)	842/7415 (11.4%)	RR 0.92 (0.84 to 1.01)	9 fewer per 1,000 (from 18 fewer to 1 more)	⊕⊕⊕◯ Moderate
Rivaroxaban 15 mg once daily	1	randomised trials	serious[d]	not serious	not serious	serious[b]	none	7/637 (1.1%)	5/637 (0.8%)	RR 1.40 (0.45 to 4.39)	3 more per 1,000 (from 4 fewer to 27 more)	⊕⊕◯◯ Low
Rivaroxaban 20 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	582/7081 (8.2%)	632/7090 (8.9%)	RR 0.92 (0.83 to 1.03)	7 fewer per 1,000 (from 15 fewer to 3 more)	⊕⊕⊕⊕ High

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to a high risk of selection bias, lack of blinding, incomplete outcome data.
[b] Downgraded due to imprecision owing to wide confidence intervals and low event rates.
[c] Downgraded due to a high risk of incomplete outcome data.
[d] Downgraded due to a high risk of selection bias.
[e] Downgraded due to inadequate blinding
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 89 GRADE evidence profile: all-cause mortality reported in the included NRSIs (as HR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOAC	VKA	Relative (95% CI)	Absolute (95% CI)	
Apixaban	4	observational studies	serious[a]	serious[b]	not serious	serious[c]	none	NR /28267	NR/81372	HR 1.16 (0.88 to 1.54)	Not estimable	⊕◯◯◯ Very low
Dabigatran	4	observational studies	serious[a]	not serious	not serious	not serious	none	NR /63166	NR /100132	HR 1.00 (0.92 to 1.09)	Not estimable	⊕⊕⊕◯ Moderate
Edoxaban	1	observational studies	very serious[d]	not serious	not serious	not serious	none	NR /2255	NR /20179	HR 1.40 (1.22 to 1.61)	Not estimable	⊕⊕◯◯ Low
Rivaroxaban	4	observational studies	serious[a]	serious[b]	not serious	not serious	none	NR /91595	NR /135927	HR 1.18 (1.05 to 1.33)	Not estimable	⊕⊕◯◯ Low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NA**: not applicable; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
[b] Downgraded due to inconsistency owing to a high degree of heterogeneity in the analysis.
[c] Downgraded due to imprecision owing to wide confidence intervals including both positive and negative relative treatment effects.
[d] Downgraded due to high risk of bias due to unmeasured confounding.
* Absolute effects were not estimable as event rates were not reported.

Table 90 GRADE evidence profile: all-cause mortality reported in the included NRSIs (as RR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	2	observational studies	serious[c]	serious[a]	not serious	serious[b]	none	970/12376 (7.8%)	6134/56299 (10.9%)	RR 0.79 (0.36 to 1.76)	23 fewer per 1,000 (from 70 fewer to 83 more)	⨁◯◯◯ Very low
Dabigatran	3	observational studies	serious[c]	not serious	not serious	not serious	none	689/8885 (7.8%)	6145/56682 (10.8%)	RR 0.82 (0.69 to 0.98)	20 fewer per 1,000 (from 34 fewer to 2 fewer)	⨁◯◯◯ Very low
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	2	observational studies	serious[c]	serious[a]	not serious	not serious	none	1921/25588 (7.5%)	6134/56299 (10.9%)	RR 0.94 (0.79 to 1.11)	7 fewer per 1,000 (from 23 fewer to 12 more)	⨁◯◯◯ Very low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to inconsistency owing to a high degree of heterogeneity in the analysis
[b] Downgraded due to imprecision owing to wide confidence intervals including both positive and negative relative treatment effects
[c] Downgraded due to high risk of bias due to unmeasured confounding
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 91 GRADE evidence profile: cardiovascular mortality reported in the included RCTs

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban 2.5 mg twice daily	NR	-	-	-	-	-	-	-	-	-	-	-
Apixaban 5 mg twice daily	1	randomised trials	very serious[a]	not serious	not serious	not serious	none	308/9120 (3.4%)	344/9081 (3.8%)	RR 0.89 (0.77 to 1.04)	4 fewer per 1,000 (from 9 fewer to 2 more)	⊕⊕◯◯ Low
Dabigatran 110 mg twice daily	1	randomised trials	serious[b]	not serious	not serious	not serious	none	289/6015 (4.8%)	317/6022 (5.3%)	RR 0.91 (0.78 to 1.07)	5 fewer per 1,000 (from 12 fewer to 4 more)	⊕⊕⊕◯ Moderate
Dabigatran 150 mg twice daily	1	randomised trials	serious[b]	not serious	not serious	not serious	none	274/6076 (4.5%)	317/6022 (5.3%)	RR 0.86 (0.73 to 1.00)	7 fewer per 1,000 (from 14 fewer to 0 fewer)	⊕⊕⊕◯ Moderate
Edoxaban 30 mg once daily	2	randomised trials	not serious	not serious	not serious	not serious	none	531/7278 (7.3%)	613/7286 (8.4%)	RR 0.87 (0.76 to 0.99)	11 fewer per 1,000 (from 20 fewer to 1 fewer)	⊕⊕⊕⊕ High
Edoxaban 60 mg once daily	2	randomised trials	not serious	not serious	not serious	not serious	none	530/7215 (7.3%)	613/7286 (8.4%)	RR 0.87 (0.77 to 0.97)	11 fewer per 1,000 (from 19 fewer to 3 fewer)	⊕⊕⊕⊕ High
Rivaroxaban 15 mg once daily	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban 20 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	170/7081 (2.4%)	193/7061 (2.7%)	RR 0.88 (0.72 to 1.08)	3 fewer per 1,000 (from 8 fewer to 2 more)	⊕⊕⊕⊕ High

Abbreviations:

CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.

Notes:

[a] Downgraded due to a high risk of selection, blinding, incomplete outcome data.

[b] Downgraded due to inadequate blinding.

* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 92 GRADE evidence profile: cardiovascular mortality reported in the included NRSIs (as HR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	1	observational studies	very serious[a]	not serious	not serious	serious[b]	none	NR/4894	NR/4894	HR 1.14 (0.96 to 1.35)	Not estimable	⊕◯◯◯ Very low
Dabigatran	1	observational studies	very serious[a]	not serious	not serious	not serious	none	NR/23654	NR/23654	HR 1.06 (0.97 to 1.16)	Not estimable	⊕◯◯◯ Very low
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	1	observational studies	very serious[a]	not serious	not serious	not serious	none	NR/59449	NR/59449	HR 1.18 (1.12 to 1.24)	Not estimable	⊕◯◯◯ Very low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
[b] Downgraded due to imprecision owing to wide confidence intervals including both positive and negative relative treatment effects
* Absolute effects were not estimable as event rates were not reported.

Table 93 GRADE evidence profile: cardiovascular mortality reported in the included NRSIs (as RR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	NR	-	-	-	-	-	-	-	-	-	-	-
Dabigatran	1	observational studies	very serious[a]	not serious	not serious	very serious[b]	none	0/383 (0.0%)	4/383 (1.0%)	RR 0.11 (0.01 to 2.06)	9 fewer per 1,000 (from 10 fewer to 11 more)	⨁◯◯◯ Very low
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	NR	-	-	-	-	-	-	-	-	-	-	-

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
[b] Downgraded due to imprecision owing to low event rates and very wide confidence intervals.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 94 GRADE evidence profile: major/life threatening bleeding reported in the included RCTs

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban 2.5 mg twice daily	1	randomised trials	very serious[a]	N/A	not serious	very serious[b]	none	0/72 (0.0%)	1/75 (1.3%)	RR 0.35 (0.01 to 8.38)	9 fewer per 1,000 (13 fewer to 98 more)	⊕◯◯◯ Very low
Apixaban 5 mg twice daily	2	randomised trials	very serious[a]	not serious	not serious	not serious	none	327/9159 (3.6%)	463/9127 (5.1%)	RR 0.70 (0.61 to 0.81)	15 fewer per 1,000 (20 fewer to 10 fewer)	⊕⊕◯◯ Low
Dabigatran 110 mg twice daily	1	randomised trials	serious[b]	not serious	not serious	not serious	none	342/6015 (5.7%)	421/6022 (7.0%)	RR 0.81 (0.71 to 0.93)	13 fewer per 1,000 (20 fewer to 5 fewer)	⊕⊕⊕◯ Moderate
Dabigatran 150 mg twice daily	2	randomised trials	serious[a]	not serious	not serious	not serious	none	399/6176 (6.5%)	421/6092 (6.9%)	RR 0.94 (0.82 to 1.07)	4 fewer per 1,000 (12 fewer to 5 more)	⊕⊕⊕◯ Moderate
Edoxaban 30 mg once daily	3	randomised trials	serious[a]	not serious	not serious	not serious	none	254/7367 (3.4%)	525/7387 (7.1%)	RR 0.49 (0.42 to 0.56)	36 fewer per 1,000 (41 fewer to 31 fewer)	⊕⊕⊕◯ Moderate
Edoxaban 60 mg once daily	3	randomised trials	serious[a]	not serious	not serious	not serious	none	421/7367 (5.7%)	525/7387 (7.1%)	RR 0.80 (0.71 to 0.91)	14 fewer per 1,000 (21 fewer to 6 fewer)	⊕⊕⊕◯ Moderate
Rivaroxaban 15 mg once daily	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban 20 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	395/7111 (5.6%)	386/7125 (5.4%)	RR 1.03 (0.89 to 1.18)	2 more per 1,000 (from 6 fewer to 10 more)	⊕⊕⊕⊕ High

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to a high risk of selection, blinding, incomplete outcome data.
[b] Downgraded due to inadequate blinding.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 95 GRADE evidence profile: major/life threatening bleeding reported in the included NRSIs (as HR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	5	observational studies	serious[a]	not serious	not serious	not serious	none	NR/27217	NR/ 423066	HR 0.63 (0.52 to 0.75)	Not estimable	⊕⊕⊕◯ Moderate
Dabigatran	5	observational studies	serious[a]	not serious	not serious	not serious	none	NR/86400	NR/ 440049	HR 0.0.75 (0.61 to 0.92)	Not estimable	⊕⊕⊕◯ Moderate
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	4	observational studies	serious[a]	not serious	not serious	not serious	none	NR/148364	NR/ 496902	HR 1.08 (1.03 to 1.13)	Not estimable	⊕⊕⊕◯ Moderate

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NA**: not applicable; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
* Absolute effects were not estimable as event rates were not reported.

Table 96 GRADE evidence profile: major/life threatening bleeding reported in the included NRSIs (as RR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	3	observational studies	serious[a]	not serious	not serious	not serious	none	224/14536 (1.5%)	1048/58459 (1.8%)	RR 0.54 (0.44 to 0.65)	8 fewer per 1,000 (from 10 fewer to 6 fewer)	⊕◯◯◯ Very low
Dabigatran	4	observational studies	very serious[d]	not serious	not serious	serious[b]	none	126/12064 (1.0%)	983/58868 (1.7%)	RR 0.64 (0.43 to 0.97)	6 fewer per 1,000 (from 10 fewer to 1 fewer)	⊕◯◯◯ Very low
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	2	observational studies	serious[c]	not serious	not serious	not serious	none	586/25588 (2.3%)	948/56299 (1.7%)	RR 0.84 (0.69 to 1.04)	3 fewer per 1,000 (from 5 fewer to 1 more)	⊕◯◯◯ Very low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
[b] Downgraded due to imprecision owing to wide confidence intervals including both positive and negative relative treatment effects.
[c] Downgraded due to high risk of bias due to unmeasured confounding.
[d] Downgraded twice due to very high risk of bias owing to a very high risk of confounding, and unclear deviations from the intended interventions.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 97 GRADE evidence profile: intracranial bleeding reported in the included RCTs

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban 2.5 mg twice daily	NR	-	-	-	-	-	-	-	-	-	-	-
Apixaban 5 mg twice daily	1	randomised trials	very serious[a]	not serious	not serious	not serious	none	52/9088 (0.6%)	122/9052 (1.3%)	RR 0.42 (0.31 to 0.59)	8 fewer per 1,000 (from 9 fewer to 6 fewer)	⊕⊕◯◯ Low
Dabigatran 110 mg twice daily	1	randomised trials	serious[d]	not serious	not serious	not serious	none	27/6015 (0.4%)	87/6022 (1.4%)	RR 0.31 (0.20 to 0.48)	10 fewer per 1,000 (from 12 fewer to 8 fewer)	⊕⊕⊕◯ Moderate
Dabigatran 150 mg twice daily	1	randomised trials	serious[d]	not serious	not serious	not serious	none	36/6076 (0.6%)	87/6022 (1.4%)	RR 0.41 (0.28 to 0.60)	9 fewer per 1,000 (from 10 fewer to 6 fewer)	⊕⊕⊕◯ Moderate
Edoxaban 30 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	41/7002 (0.6%)	132/7012 (1.9%)	RR 0.31 (0.22 to 0.44)	13 fewer per 1,000 (from 15 fewer to 11 fewer)	⊕⊕⊕⊕ High
Edoxaban 60 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	61/7120 (0.9%)	132/7012 (1.9%)	RR 0.46 (0.34 to 0.62)	10 fewer per 1,000 (from 12 fewer to 7 fewer)	⊕⊕⊕⊕ High
Rivaroxaban 15 mg once daily	1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	5/639 (0.8%)	10/639 (1.6%)	RR 0.50 (0.17 to 1.45)	8 fewer per 1,000 (from 13 fewer to 7 more)	⊕⊕◯◯ Low
Rivaroxaban 20 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	55/7111 (0.8%)	84/7125 (1.2%)	RR 0.66 (0.47 to 0.92)	4 fewer per 1,000 (from 6 fewer to 1 fewer)	⊕⊕⊕⊕ High

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to a high risk of selection, blinding, incomplete outcome data.
[b] Downgraded due to imprecision owing to wide confidence intervals and low event rates.
[c] Downgraded due to a high risk of selection bias.
[d] Downgraded due to inadequate blinding.

* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 98 GRADE evidence profile: intracranial bleeding reported in the included NRSIs (as HR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	4	observational studies	serious[a]	not serious	not serious	not serious	none	NR/24997	NR/ 442347	HR 0.55 (0.42 to 0.72)	Not estimable	⊕⊕⊕◯ Moderate
Dabigatran	4	observational studies	serious[a]	not serious	not serious	not serious	none	NR/86017	NR/ 461107	HR 0.52 (0.36 to 0.73)	Not estimable	⊕⊕⊕◯ Moderate
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	4	observational studies	serious[a]	not serious	not serious	not serious	none	NR/148364	NR/ 496902	HR 0.69 (0.58 to 0.81)	Not estimable	⊕⊕⊕◯ Moderate

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NA**: not applicable; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
* Absolute effects were not estimable as event rates were not reported.

Table 99 GRADE evidence profile: intracranial bleeding reported in the included NRSIs (as RR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	2	observational studies	serious[a]	not serious	not serious	not serious	none	53/14536 (0.4%)	616/58459 (1.1%)	RR 0.46 (0.34 to 0.61)	6 fewer per 1,000 (from 7 fewer to 4 fewer)	⨁◯◯◯ Very low
Dabigatran	2	observational studies	serious[a]	serious[b]	not serious	serious[c]	none	58/8885 (0.7%)	607/56682 (1.1%)	RR 0.90 (0.36 to 2.26)	1 fewer per 1,000 (from 7 fewer to 13 more)	⨁◯◯◯ Very low
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	1	observational studies	very serious[a]	not serious	not serious	not serious	none	127/25588 (0.5%)	605/56299 (1.1%)	RR 0.58 (0.42 to 0.80)	5 fewer per 1,000 (from 6 fewer to 2 fewer)	⨁◯◯◯ Very low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
[b] Downgraded due to inconsistency owing to a high degree of heterogeneity in the analysis.
[c] Downgraded due to imprecision owing to wide confidence intervals including both positive and negative relative treatment effects.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 100 GRADE evidence profile: gastrointestinal bleeding reported in the included RCTs

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban 2.5 mg twice daily	NR	-	-	-	-	-	-	-	-	-	-	-
Apixaban 5 mg twice daily	1	randomised trials	very serious[a]	not serious	not serious	not serious	none	105/9088 (1.2%)	119/9052 (1.3%)	RR 0.88 (0.68 to 1.14)	2 fewer per 1,000 (from 4 fewer to 2 more)	⊕⊕◯◯ Low
Dabigatran 110 mg twice daily	1	randomised trials	serious[d]	not serious	not serious	not serious	none	137/6015 (2.3%)	126/6022 (2.1%)	RR 1.09 (0.86 to 1.38)	2 more per 1,000 (from 3 fewer to 8 more)	⊕⊕⊕◯ Moderate
Dabigatran 150 mg twice daily	1	randomised trials	serious[d]	not serious	not serious	not serious	none	188/6076 (3.1%)	126/6022 (2.1%)	RR 1.48 (1.18 to 1.85)	10 more per 1,000 (from 4 more to 18 more)	⊕⊕⊕◯ Moderate
Edoxaban 30 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	129/7002 (1.8%)	190/7012 (2.7%)	RR 0.68 (0.55 to 0.85)	9 fewer per 1,000 (from 12 fewer to 4 fewer)	⊕⊕⊕⊕ High
Edoxaban 60 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	232/7012 (3.3%)	190/7012 (2.7%)	RR 1.22 (1.01 to 1.47)	6 more per 1,000 (from 0 fewer to 13 more)	⊕⊕⊕⊕ High
Rivaroxaban 15 mg once daily	1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	6/639 (0.9%)	12/639 (1.9%)	RR 0.50 (0.19 to 1.32)	9 fewer per 1,000 (from 15 fewer to 6 more)	⊕⊕◯◯ Low
Rivaroxaban 20 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	224/7111 (3.2%)	154/7125 (2.2%)	RR 1.46 (1.19 to 1.78)	10 more per 1,000 (from 4 more to 17 more)	⊕⊕⊕⊕ High

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to a high risk of selection, blinding, incomplete outcome data.
[b] Downgraded due to imprecision owing to wide confidence intervals and low event rates.
[c] Downgraded due to a high risk of selection bias.
[d] Downgraded due to inadequate blinding.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 101 GRADE evidence profile: gastrointestinal bleeding reported in the included NRSIs (as HR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	4	observational studies	serious[a]	not serious	not serious	not serious	none	NR/24997	NR/ 442347	HR 0.74 (0.66 to 0.82)	Not estimable	⊕⊕⊕◯ Moderate
Dabigatran	4	observational studies	serious[a]	not serious	not serious	not serious	none	NR/86017	NR/ 442347	HR 1.15 (1.05 to 1.25)	Not estimable	⊕⊕⊕◯ Moderate
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	4	observational studies	serious[a]	not serious	not serious	not serious	none	NR/148364	NR/ 442347	HR 1.28 (1.19 to 1.37)	Not estimable	⊕⊕⊕◯ Moderate

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
* Absolute effects were not estimable as event rates were not reported.

Table 102 GRADE evidence profile: gastrointestinal bleeding reported in the included NRSIs (as RR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	3	observational studies	serious[a]	serious[b]	not serious	not serious	none	262/14536 (1.8%)	1281/37459 (3.4%)	RR 0.25 (0.06 to 0.99)	26 fewer per 1,000 (from 32 fewer to 0 fewer)	⊕◯◯◯ Very low
Dabigatran	3	observational studies	serious[a]	not serious	not serious	not serious	none	183/8950 (2.0%)	1217/56682 (2.1%)	RR 0.89 (0.60 to 1.33)	2 fewer per 1,000 (from 9 fewer to 7 more)	⊕◯◯◯ Very low
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	2	observational studies	serious[a]	serious[b]	not serious	not serious	none	798/25588 (3.1%)	1212/56299 (2.2%)	RR 0.95 (0.66 to 1.38)	1 fewer per 1,000 (from 7 fewer to 8 more)	⊕◯◯◯ Very low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
[b] Downgraded due to inconsistency owing to a high degree of heterogeneity in the analysis.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 103 GRADE evidence profile: clinically-relevant bleeding reported in the included RCTs

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban 2.5 mg twice daily	1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	1/72 (1.4%)	3/75 (4.0%)	RR 0.35 (0.04 to 3.26)	26 fewer per 1,000 (from 38 fewer to 90 more)	⊕◯◯◯ Very low
Apixaban 5 mg twice daily	1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	1/71 (1.4%)	3/75 (4.0%)	RR 0.35 (0.04 to 3.31)	26 fewer per 1,000 (from 38 fewer to 92 more)	⊕◯◯◯ Very low
Dabigatran 110 mg twice daily	NR	-	-	-	-	-	-	-	-	-	-	-
Dabigatran 150 mg twice daily	1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	9/100 (9.0%)	4/100 (4.0%)	RR 1.57 (0.50 to 4.91)	23 fewer per 1,000 (from 20 fewer to 156 more)	⊕◯◯◯ Very low
Edoxaban 30 mg once daily	2	randomised trials	serious	not serious	not serious	not serious	none	976/7237 (13.5%)	1403/7262 (19.3%)	RR 0.70 (0.65 to 0.75)	58 fewer per 1,000 (from 68 fewer to 48 fewer)	⊕⊕⊕⊕ High
Edoxaban 60 mg once daily	2	randomised trials	serious	not serious	not serious	not serious	none	1222/7246 (16.9%)	1403/7262 (19.3%)	RR 0.87 (0.81 to 0.93)	25 fewer per 1,000 (from 37 fewer to 14 fewer)	⊕⊕⊕⊕ High
Rivaroxaban 15 mg once daily	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban 20 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	1185/7111 (16.7%)	1115/7125 (15.6%)	RR 1.06 (0.99 to 1.15)	9 more per 1,000 (from 2 fewer to 23 more)	⊕⊕⊕⊕ High

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to a high risk of selection, blinding, incomplete outcome data.
[b] Downgraded due to imprecision owing to very wide confidence intervals and low event rates.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 104 GRADE evidence profile: clinically-relevant bleeding reported in the included NRSIs (as HR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	3	observational studies	very serious[a]	not serious	not serious	not serious	none	NR/148724	NR/391299	HR 0.73 (0.69 to 0.78)	Not estimable	⊕⊕◯◯ Low
Dabigatran	3	observational studies	very serious[a]	not serious	not serious	not serious	none	NR/60269	NR/391299	HR 0.85 (0.83 to 0.87)	Not estimable	⊕⊕◯◯ Low
Edoxaban	2	observational studies	very serious[a]	not serious	not serious	serious[b]	none	NR/15521	NR/367476	HR 0.82 (0.64 to 1.04)	Not estimable	⊕◯◯◯ Very low
Rivaroxaban	3	observational studies	very serious[a]	not serious	not serious	not serious	none	NR/375998	NR/391299	HR 1.07 (1.00 to 1.15)	Not estimable	⊕⊕◯◯ Low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
[b] Downgraded due to imprecision owing to wide confidence intervals including both positive and negative relative treatment effects.
* Absolute effects were not estimable as event rates were not reported.

Table 105 GRADE evidence profile: clinically-relevant bleeding reported in the included NRSIs (as RR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	1	observational studies	very serious[a]	not serious	not serious	not serious	none	822/10117 (8.1%)	2573/23823 (10.8%)	RR 0.75 (0.70 to 0.81)	27 fewer per 1,000 (from 32 fewer to 21 fewer)	⊕⊕◯◯ Low
Dabigatran	1	observational studies	very serious[a]	not serious	not serious	not serious	none	393/5122 (7.7%)	2573/23823 (10.8%)	RR 0.71 (0.64 to 0.79)	31 fewer per 1,000 (from 39 fewer to 23 fewer)	⊕⊕◯◯ Low
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	1	observational studies	very serious[a]	not serious	not serious	not serious	none	2276/22143 (10.3%)	2573/23823 (10.8%)	RR 0.95 (0.90 to 1.00)	5 fewer per 1,000 (from 11 fewer to 0 fewer)	⊕⊕◯◯ Low

Abbreviations:

CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **RR**: risk ratio; **VKA**; vitamin K antagonist.

Notes:

[a] Downgraded due to high risk of bias due to unmeasured confounding.

* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 106 GRADE evidence profile: stroke and systemic embolic events reported in the included RCTs

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban 2.5 mg twice daily	1	randomised trials	very serious[a]	not serious	not serious	very serious[d]	none	0/72 (0.0%)	4/75 (5.3%)	RR 0.12 (0.01 to 2.11)	47 fewer per 1,000 (from 53 fewer to 59 more)	⊕◯◯◯ Very low
Apixaban 5 mg twice daily	2	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	212/9191 (2.3%)	269/9156 (2.9%)	RR 0.54 (0.12 to 2.45)	14 fewer per 1,000 (from 26 fewer to 43 more)	⊕◯◯◯ Very low
Dabigatran 110 mg twice daily	1	randomised trials	serious[g]	not serious	not serious	not serious	none	183/6015 (3.0%)	202/6022 (3.4%)	RR 0.91 (0.74 to 1.10)	3 fewer per 1,000 (from 9 fewer to 3 more)	⊕⊕⊕◯ Moderate
Dabigatran 150 mg twice daily	2	randomised trials	serious[a]	not serious	not serious	not serious	none	183/6125 (3.0%)	202/6092 (3.3%)	RR 0.91 (0.74 to 1.10)	3 fewer per 1,000 (from 9 fewer to 3 more)	⊕⊕⊕◯ Moderate
Edoxaban 30 mg once daily	3	randomised trials	serious[a]	serious[e]	not serious	serious[f]	none	384/7399 (5.2%)	341/7415 (4.6%)	RR 0.84 (0.27 to 2.67)	7 fewer per 1,000 (from 34 fewer to 77 more)	⊕◯◯◯ Very low
Edoxaban 60 mg once daily	3	randomised trials	serious[a]	not serious	not serious	serious[f]	none	297/7399 (4.0%)	341/7415 (4.6%)	RR 0.81 (0.46 to 1.44)	9 fewer per 1,000 (from 25 fewer to 20 more)	⊕⊕◯◯ Low
Rivaroxaban 15 mg once daily	1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	11/637 (1.7%)	22/637 (3.5%)	RR 0.50 (0.24 to 1.02)	17 fewer per 1,000 (from 26 fewer to 1 more)	⊕⊕◯◯ Low
Rivaroxaban 20 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	269/7081 (3.8%)	306/7090 (4.3%)	RR 0.88 (0.75 to 1.03)	5 fewer per 1,000 (from 11 fewer to 1 more)	⊕⊕⊕⊕ High

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to a high risk of selection bias, lack of blinding, incomplete outcome data.[b] Downgraded due to imprecision owing to wide confidence intervals and low event rates.
[c] Downgraded due to a high risk of selection bias.
[d] Downgraded due to imprecision owing to very wide confidence intervals and low event rates.
[e] Downgraded due to inconsistency owing to the presence moderate heterogeneity.
[f] Downgraded due to imprecision owing to small study effects impacting the variance in the effect estimate.
[g] Downgraded due to inadequate blinding.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 107 GRADE evidence profile: stroke and systemic embolic events reported in the included NRSIs (as HR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	4	observational studies	very serious[a]	serious[b]	not serious	serious[c]	none	NR/156143	NR/393459	HR 0.83 (0.58 to 1.19)	Not estimable	⊕◯◯◯ Very low
Dabigatran	4	observational studies	very serious[a]	not serious	not serious	not serious	none	NR/60215	NR/391682	HR 0.89 (0.78 to 1.03)	Not estimable	⊕⊕◯◯ Low
Edoxaban	2	observational studies	very serious[a]	serious[b]	not serious	serious[c]	none	NR/16811	NR/367476	HR 0.61 (0.15 to 2.57)	Not estimable	⊕◯◯◯ Very low
Rivaroxaban	3	observational studies	very serious[a]	serious[b]	not serious	serious[c]	none	NR/257214	NR/391299	HR 0.95 (0.78 to 1.15)	Not estimable	⊕◯◯◯ Very low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
[b] Downgraded due to inconsistency owing to a high degree of heterogeneity in the analysis.
[c] Downgraded due to imprecision owing to wide confidence intervals including both positive and negative relative treatment effects.
* Absolute effects were not estimable as event rates were not reported.

Table 108 GRADE evidence profile: stroke and systemic embolic events reported in the included NRSIs (as RR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	2	observational studies	serious[a]	serious[b]	not serious	not serious	none	270/12277 (2.2%)	677/25983 (2.6%)	RR 0.72 (0.45 to 1.15)	7 fewer per 1,000 (from 14 fewer to 4 more)	⊕◯◯◯ Very low
Dabigatran	2	observational studies	serious[a]	not serious	not serious	not serious	none	108/5505 (2.0%)	604/24206 (2.5%)	RR 0.80 (0.65 to 0.98)	5 fewer per 1,000 (from 9 fewer to 0 fewer)	⊕◯◯◯ Very low
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	1	observational studies	very serious[c]	not serious	not serious	not serious	none	456/22143 (2.1%)	597/23823 (2.5%)	RR 0.82 (0.73 to 0.93)	5 fewer per 1,000 (from 7 fewer to 2 fewer)	⊕◯◯◯ Very low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
[b] Downgraded due to inconsistency owing to a high degree of heterogeneity in the analysis.
[c] Downgraded due to high risk of bias due to unmeasured confounding.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 109 GRADE evidence profile: ischaemic stroke reported in the included RCTs

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban 2.5 mg twice daily	NR	-	-	-	-	-	-	-	-	-	-	-
Apixaban 5 mg twice daily	1	randomised trials	very serious[a]	not serious	not serious	not serious	none	162/9120 (1.8%)	175/9081 (1.9%)	RR 0.92 (0.75 to 1.14)	2 fewer per 1,000 (from 5 fewer to 3 more)	⊕⊕◯◯ Low
Dabigatran 110 mg twice daily	1	randomised trials	serious[d]	not serious	not serious	not serious	none	159/6015 (2.6%)	142/6022 (2.4%)	RR 1.12 (0.90 to 1.40)	3 more per 1,000 (from 2 fewer to 9 more)	⊕⊕⊕◯ Moderate
Dabigatran 150 mg twice daily	1	randomised trials	serious[d]	not serious	not serious	not serious	none	111/6076 (1.8%)	142/6022 (2.4%)	RR 0.77 (0.61 to 0.99)	5 fewer per 1,000 (from 9 fewer to 0 fewer)	⊕⊕⊕◯ Moderate
Edoxaban 30 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	333/7034 (4.7%)	235/7036 (3.3%)	RR 1.42 (1.20 to 1.76)	14 more per 1,000 (from 7 more to 25 more)	⊕⊕⊕⊕ High
Edoxaban 60 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	236/7035 (3.4%)	235/7036 (3.3%)	RR 1.00 (0.84 to 1.20)	0 fewer per 1,000 (from 5 fewer to 7 more)	⊕⊕⊕⊕ High
Rivaroxaban 15 mg once daily	1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	7/639 (1.1%)	17/639 (2.7%)	RR 0.41 (0.17 to 0.99)	16 fewer per 1,000 (from 22 fewer to 0 fewer)	⊕⊕◯◯ Low
Rivaroxaban 20 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	149/7111 (2.1%)	161/7764 (2.1%)	RR 0.93 (0.74 to 1.16)	1 fewer per 1,000 (from 5 fewer to 3 more)	⊕⊕⊕⊕ High

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to a high risk of selection, blinding, incomplete outcome data.
[b] Downgraded due to imprecision owing to wide confidence intervals and low event rates.
[c] Downgraded due to a high risk of selection bias.
[d] Downgraded due to inadequate blinding.

* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 110 GRADE evidence profile: ischaemic stroke reported in the included NRSIs (as HR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	5	observational studies	very serious[a]	serious[b]	not serious	serious[c]	none	NR/157866	NR/789644	HR 1.21 (0.89 to 1.66)	Not estimable	⊕◯◯◯ Very low
Dabigatran	5	observational studies	very serious[a]	serious[b]	not serious	serious[c]	none	NR/310866	NR/804929	HR 1.14 (0.80 to 1.64)	Not estimable	⊕◯◯◯ Very low
Edoxaban	1	observational studies	very serious[a]	not serious	not serious	serious[c]	none	NR/14276	NR/347240	HR 0.88 (0.74 to 1.05)	Not estimable	⊕◯◯◯ Very low
Rivaroxaban	5	observational studies	very serious[a]	not serious	not serious	not serious	none	NR/376964	NR/844142	HR 1.04 (0.96 to 1.14)	Not estimable	⊕◯◯◯ Very low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
[b] Downgraded due to inconsistency owing to a high degree of heterogeneity in the analysis.
[c] Downgraded due to imprecision owing to wide confidence intervals including both positive and negative relative treatment effects.
* Absolute effects were not estimable as event rates were not reported.

Table 111 GRADE evidence profile: ischaemic stroke reported in the included NRSIs (as RR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	3	observational studies	serious[a]	not serious	not serious	not serious	none	230/14536 (1.6%)	1086/58459 (1.9%)	RR 0.76 (0.53 to 1.09)	4 fewer per 1,000 (from 9 fewer to 2 more)	⊕◯◯◯ Very low
Dabigatran	3	observational studies	serious[a]	not serious	not serious	not serious	none	159/8885 (1.8%)	1029/56682 (1.8%)	RR 1.04 (0.88 to 1.23)	1 more per 1,000 (from 2 fewer to 4 more)	⊕◯◯◯ Very low
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	2	observational studies	serious[a]	not serious	not serious	not serious	none	381/25588 (1.5%)	1026/56299 (1.8%)	RR 0.87 (0.77 to 0.99)	2 fewer per 1,000 (from 4 fewer to 0 fewer)	⊕◯◯◯ Very low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 112 GRADE evidence profile: haemorrhagic stroke reported in the included NRSIs (as HR)

Intervention	Certainty assessment									Effect		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	1	observational studies	very serious[a]	not serious	not serious	not serious	none	NR/10117	NR/23823	HR 0.39 (0.23 to 0.66)	Not estimable	⊕⊕◯◯ Low
Dabigatran	1	observational studies	very serious[a]	not serious	not serious	not serious	none	NR/10117	NR/23823	HR 0.27 (0.14 to 0.52)	Not estimable	⊕⊕◯◯ Low
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	1	observational studies	very serious[a]	not serious	not serious	not serious	none	NR/10117	NR/23823	HR 0.79 (0.58 to 1.08)	Not estimable	⊕⊕◯◯ Low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding.
* Absolute effects were not estimable as event rates were not reported.

Table 113 GRADE evidence profile: haemorrhagic stroke reported in the included NRSIs (as RR)

Intervention	Certainty assessment									Effect		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	1	observational studies	very serious[a]	not serious	not serious	not serious	none	25/10117 (0.2%)	119/23823 (0.5%)	RR 0.49 (0.32 to 0.76)	3 fewer per 1,000 (from 3 fewer to 1 fewer)	⊕⊕◯◯ Low
Dabigatran	1	observational studies	very serious[a]	not serious	not serious	not serious	none	10/5122 (0.2%)	119/23823 (0.5%)	RR 0.39 (0.21 to 0.74)	3 fewer per 1,000 (from 4 fewer to 1 fewer)	⊕⊕◯◯ Low
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	1	observational studies	very serious[a]	not serious	not serious	not serious	none	78/22143 (0.4%)	119/23823 (0.5%)	RR 0.71 (0.53 to 0.94)	1 fewer per 1,000 (from 2 fewer to 0 fewer)	⊕⊕◯◯ Low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 114 GRADE evidence profile: haemorrhagic stroke reported in the included RCTs

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban 2.5 mg twice daily	NR	-	-	-	-	-	-	-	-	-	-	-
Apixaban 5 mg twice daily	1	randomised trials	serious[b]	not serious	not serious	not serious	none	40/9120 (0.4%)	78/9081 (0.9%)	RR 0.51 (0.35 to 0.75)	4 fewer per 1,000 (from 6 fewer to 2 fewer)	⊕⊕⊕◯ Moderate
Dabigatran 110 mg twice daily	1	randomised trials	serious[c]	not serious	not serious	not serious	none	14/6015 (0.2%)	45/6022 (0.7%)	RR 0.31 (0.17 to 0.57)	5 fewer per 1,000 (from 6 fewer to 3 fewer)	⊕⊕⊕◯ Moderate
Dabigatran 150 mg twice daily	1	randomised trials	serious[c]	not serious	not serious	not serious	none	12/6076 (0.2%)	45/6022 (0.7%)	RR 0.26 (0.14 to 0.50)	6 fewer per 1,000 (from 6 fewer to 4 fewer)	⊕⊕⊕◯ Moderate
Edoxaban 30 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	30/7034 (0.4%)	90/7036 (1.3%)	RR 0.33 (0.22 to 0.50)	9 fewer per 1,000 (from 10 fewer to 6 fewer)	⊕⊕⊕⊕ High
Edoxaban 60 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	49/7035 (0.7%)	90/7036 (1.3%)	RR 0.54 (0.39 to 0.77)	6 fewer per 1,000 (from 8 fewer to 3 fewer)	⊕⊕⊕⊕ High
Rivaroxaban 15 mg once daily	1	randomised trials	serious[b]	not serious	not serious	serious[a]	none	3/639 (0.5%)	4/639 (0.6%)	RR 0.75 (0.17 to 3.34)	2 fewer per 1,000 (from 5 fewer to 15 more)	⊕⊕◯◯ Low
Rivaroxaban 20 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	29/7081 (0.4%)	50/7090 (0.7%)	RR 0.58 (0.37 to 0.92)	3 fewer per 1,000 (from 4 fewer to 1 fewer)	⊕⊕⊕⊕ High

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to imprecision owing to wide confidence intervals and low event rates.
[b] Downgraded due to a high risk of selection bias.
[c] Downgraded due to inadequate blinding.

* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 115 GRADE evidence profile: adherence reported in the included RCTs

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban 2.5 mg twice daily	NR	-	-	-	-	-	-	-	-	-	-	-
Apixaban 5 mg twice daily	NR	-	-	-	-	-	-	-	-	-	-	-
Dabigatran 110 mg twice daily	NR	-	-	-	-	-	-	-	-	-	-	-
Dabigatran 150 mg twice daily	NR	-	-	-	-	-	-	-	-	-	-	-
Edoxaban 30 mg once daily	NR	-	-	-	-	-	-	-	-	-	-	-
Edoxaban 60 mg once daily	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban 15 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	6977/7111 (98.1%)	6961/7125 (97.7%)	RR 1.00 (1.00 to 1.01)	0 fewer per 1,000 (from 0 fewer to 10 more)	⊕⊕⊕⊕ High
Rivaroxaban 20 mg once daily	NR	-	-	-	-	-	-	-	-	-	-	-

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 116 GRADE evidence profile: adherence reported in the included NRSIs

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	NR	-	-	-	-	-	-	-	-	-	-	-
Dabigatran	NR	-	-	-	-	-	-	-	-	-	-	-
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	NR	-	-	-	-	-	-	-	-	-	-	-

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.

Table 117 GRADE evidence profile: persistence reported in the included RCTs

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban 2.5 mg twice daily	1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	67/74 (90.5%)	65/74 (87.8%)	RR 1.03 (0.92 to 1.15)	26 more per 1,000 (from 70 fewer to 132 more)	⊕◯◯◯ Very low
Apixaban 5 mg twice daily	2	randomised trials	very serious[a]	not serious	not serious	not serious	none	7210/9194 (78.4%)	7002/9155 (76.5%)	RR 1.03 (1.01 to 1.04)	23 more per 1,000 (from 8 more to 31 more)	⊕⊕◯◯ Low
Dabigatran 110 mg twice daily	1	randomised trials	serious[d]	not serious	not serious	not serious	none	4854/6015 (80.7%)	5120/6022 (85.0%)	RR 0.95 (0.93 to 0.96)	43 fewer per 1,000 (from 60 fewer to 34 fewer)	⊕⊕⊕◯ Moderate
Dabigatran 150 mg twice daily	1	randomised trials	serious[d]	not serious	not serious	not serious	none	4865/6076 (80.1%)	5120/6022 (85.0%)	RR 0.94 (0.93 to 0.96)	51 fewer per 1,000 (from 60 fewer to 34 fewer)	⊕⊕⊕◯ Moderate
Edoxaban 30 mg once daily	3	randomised trials	serious[a]	serious[c]	not serious	not serious	none	6615/7414 (87.6%)	6532/7421 (88.0%)	RR 1.01 (0.99 to 1.02)	0 fewer per 1,000 (from 44 fewer to 44 more)	⊕⊕◯◯ Low
Edoxaban 60 mg once daily	3	randomised trials	serious[a]	not serious	not serious	not serious	none	6527/7347 (88.8%)	6532/7421 (88.0%)	RR 1.01 (1.00 to 1.02)	0 fewer per 1,000 (from 26 fewer to 35 more)	⊕⊕⊕◯ Moderate
Rivaroxaban 15 mg once daily	1	randomised trials	serious[a]	not serious	not serious	not serious	none	637/640 (99.5%)	637/640 (99.5%)	RR 1.00 (0.99 to 1.01)	0 fewer per 1,000 (from 10 fewer to 10 more)	⊕⊕⊕◯ Moderate
Rivaroxaban 20 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	5440/7131 (76.3%)	5549/7133 (77.8%)	RR 0.98 (0.96 to 1.00)	16 fewer per 1,000 (from 31 fewer to 0 fewer)	⊕⊕⊕⊕ High

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to a high risk of selection bias, lack of blinding, incomplete outcome data.[b] Downgraded due to imprecision owing to wide confidence intervals and low event rates.
[c] Downgraded due to inconsistency owing to the presence moderate heterogeneity.
[d] Downgraded due to inadequate blinding.

* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 118 GRADE evidence profile: persistence reported in the included NRSIs (as HR)

Intervention	Certainty assessment									Effect		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	NR	-	-	-	-	-	-	-	-	-	-	-
Dabigatran	NR	-	-	-	-	-	-	-	-	-	-	-
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	NR	-	-	-	-	-	-	-	-	-	-	-

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.

Table 119 GRADE evidence profile: persistence reported in the included NRSIs (as RR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	2	observational studies	serious[a]	serious[b]	not serious	serious[c]	none	6532/16038 (40.7%)	7760/12239 (63.4%)	RR 0.81 (0.40 to 1.67)	120 fewer per 1,000 (from 380 fewer to 425 more)	⊕◯◯◯ Very low
Dabigatran	1	observational studies	very serious[a]	not serious	not serious	not serious	none	6443/29288 (22.0%)	6451/10079 (64.0%)	RR 0.34 (0.33 to 0.35)	422 fewer per 1,000 (from 429 fewer to 416 fewer)	⊕⊕◯◯ Low
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	1	observational studies	very serious[a]	not serious	not serious	not serious	none	16742/34167 (49.0%)	6451/10079 (64.0%)	RR 0.77 (0.75 to 0.78)	147 fewer per 1,000 (from 160 fewer to 141 fewer)	⊕⊕◯◯ Low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
[b] Downgraded due to inconsistency owing to a high degree of heterogeneity in the analysis.
[c] Downgraded due to imprecision owing to wide confidence intervals including both positive and negative relative treatment effects.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 120 GRADE evidence profile: health-related quality of life reported in the included RCTs[a]

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban 2.5 mg twice daily	NR	-	-	-	-	-	-	-	-	-	-	-
Apixaban 5 mg twice daily	NR	-	-	-	-	-	-	-	-	-	-	-
Dabigatran 110 mg twice daily	1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	497	453	-	MD 0.5 lower (4.95 lower to 3.95 higher)	⨁⨁◯◯ Low
Dabigatran 150 mg twice daily	1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	485	453	-	MD 1.7 lower (5.59 lower to 2.19 higher)	⨁⨁◯◯ Low
Edoxaban 30 mg once daily	NR	-	-	-	-	-	-	-	-	-	-	-
Edoxaban 60 mg once daily	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban 15 mg once daily	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban 20 mg once daily	NR	-	-	-	-	-	-	-	-	-	-	-

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] HRQOL was not reported by any of the included NRSIs, and as such a GRADE evidence profile table is not presented.
[b] Downgraded due to imprecision owing to small sample sizes and wide variance.
[c] Downgraded due to inadequate blinding.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 121 GRADE evidence profile: treatment discontinuation due to adverse events reported in the included RCTs

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban 2.5 mg twice daily	1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	4/72 (5.6%)	4/75 (5.3%)	RR 1.04 (0.27 to 4.01)	2 more per 1,000 (from 39 fewer to 161 more)	⊕◯◯◯ Very low
Apixaban 5 mg twice daily	2	randomised trials	very serious[a]	not serious	not serious	not serious	none	683/9191 (7.4%)	742/9156 (8.1%)	RR 0.92 (0.83 to 1.01)	6 fewer per 1,000 (from 14 fewer to 1 more)	⊕⊕◯◯ Low
Dabigatran 110 mg twice daily	1	randomised trials	serious[c]	not serious	not serious	not serious	none	355/6015 (5.9%)	235/6022 (3.9%)	RR 1.51 (1.29 to 1.78)	20 more per 1,000 (from 11 more to 30 more)	⊕⊕⊕◯ Moderate
Dabigatran 150 mg twice daily	2	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	339/6245 (5.4%)	235/6092 (3.9%)	RR 1.83 (0.53 to 6.33)	32 more per 1,000 (from 18 fewer to 208 more)	⊕◯◯◯ Very low
Edoxaban 30 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	1093/7034 (15.5%)	1168/7036 (16.6%)	RR 0.94 (0.87 to 1.01)	10 fewer per 1,000 (from 22 fewer to 2 more)	⊕⊕⊕⊕ High
Edoxaban 60 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	1204/7035 (17.1%)	1168/7036 (16.6%)	RR 1.03 (0.96 to 1.11)	5 more per 1,000 (from 7 fewer to 18 more)	⊕⊕⊕⊕ High
Rivaroxaban 15 mg once daily	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban 20 mg once daily	1	randomised trials	not serious	not serious	not serious	not serious	none	594/7131 (8.3%)	498/7133 (7.0%)	RR 1.19 (1.06 to 1.34)	13 more per 1,000 (from 4 more to 24 more)	⊕⊕⊕⊕ High

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:

[a] Downgraded due to a high risk of selection, blinding, incomplete outcome data.
[b] Downgraded due to imprecision owing to wide confidence intervals and low event rates.
[c] Downgraded due to inadequate blinding.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

Table 122 GRADE evidence profile: treatment discontinuation due to adverse events reported in the included NRSIs (as HR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	NR	-	-	-	-	-	-	-	-	-	-	-
Dabigatran	NR	-	-	-	-	-	-	-	-	-	-	-
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	NR	-	-	-	-	-	-	-	-	-	-	-

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.

Table 123 GRADE evidence profile: treatment discontinuation due to adverse events reported in the included NRSIs (as RR)

Intervention	Certainty assessment									Effect*		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)	
Apixaban	1	observational studies	very serious[a]	not serious	not serious	not serious	none	1625/4894 (33.2%)	18039/87997 (20.5%)	RR 1.62 (1.55 to 1.69)	127 more per 1,000 (from 113 more to 141 more)	⨁⨁◯◯ Low
Dabigatran	2	observational studies	very serious[a]	serious[b]	not serious	serious[c]	none	8689/26833 (32.4%)	18043/90183 (20.0%)	RR 2.77 (0.94 to 8.11)	354 more per 1,000 (from 12 fewer to 1,000 more)	⨁◯◯◯ Very low
Edoxaban	NR	-	-	-	-	-	-	-	-	-	-	-
Rivaroxaban	1	observational studies	very serious[a]	not serious	not serious	not serious	none	2835/9449 (30.0%)	18039/87997 (20.5%)	RR 1.46 (1.42 to 1.51)	94 more per 1,000 (from 86 more to 105 more)	⨁⨁◯◯ Low

Abbreviations:
CI: confidence interval; **DOAC**: direct oral anticoagulant; **HR**: hazard Ratio; **MD**: mean difference; **NR**: not reported; **RR**: risk ratio; **VKA**; vitamin K antagonist.
Notes:
[a] Downgraded due to high risk of bias due to unmeasured confounding and deviations from interventions.
[b] Downgraded due to inconsistency owing to a high degree of heterogeneity in the analysis.
[c] Downgraded due to imprecision owing to wide confidence intervals including both positive and negative relative treatment effects.
* The basis for the risk in the control group comes from a weighted average of the absolute risk observed in the control group of the included studies for each drug comparison. Relative effects are based on the meta-analysis results.

17 Appendix D: Economic appendices

17.1 Economic literature review appendices

17.1.1 Adaptations of the reference models

Table 124 List of studies adapting one of the identified reference models

Reference Model	Countries of use (adaptations)
Bayer [103,155,156]	Belgium (RIV vs warfarin)[103] France (RIV vs VKA)[110] Greece (RIV vs acenocoumarol)[115] Japan (RIV vs warfarin)[123] The UK (RIV / API vs VKA)[141] Portugal (RIV vs warfarin)[132]
Dorian [142,157]	Finland (API vs, warfarin);[106] (API vs warfarin / DAB / RIV)[107] France (API, DAB, RIV, warfarin, and ASA; frontier analysis)[111] The Netherlands (API vs VKAs);[127] (API vs VKA / DAB / RIV / EDO)[125] Japan (API vs warfarin)[124] Greece (API vs warfarin / ASA)[117] Sweden (API vs warfarin; API vs ASA)[139] Spain (API vs acenocoumarol)[137] Belgium (API, DAB, RIV, vs warfarin; and frontier analysis)[104] Portugal (API vs DAB, RIV, warfarin; and frontier analysis)[131]
López-López [44,158,159]	Austria (API vs warfarin / DAB / RIV / EDO)[100] Italy (API / DAB / RIV vs warfarin)[153]
Sorensen [143,160-162]	Belgium (DAB vs VKA)[102] France (DAB vs VKAs)[108,109] Greece (DAB vs warfarin, acenocoumarol, ASA, ASA + clopidogrel)[116] Italy (DAB vs warfarin, API, RIV)[121] Switzerland (DAB vs VKA)[140] The Netherlands (DAB vs VKA)[126] The UK (DAB vs warfarin, API, RIV)[143] United States (DAB vs warfarin)[152]

Abbreviations:
AF: atrial fibrillation; **API**: apixaban; **ASA**: aspirin; **CE**: cost-effectiveness; **DAB**: dabigatran; **EDO**: edoxaban; **MI**: myocardial infarction; **NICE**: National Institute for Health and Care Excellence; **NVAF**: non-valvular atrial fibrillation; **RIV**: rivaroxaban; **SE**: systemic embolism; **QOL**: quality of life; **TA**: technology appraisal; **VKA**: vitamin K antagonist.

17.2 Summary of economic model assumptions

Key structural assumptions underpinning the economic evaluation are summarised in ***Table 125***.

Table 125 List of key model assumptions

Assumption	Comment
Neither MI nor TIA were included in the model structure.	This decision was made in alignment with the PICO of this HTA, which was developed in accordance with standard outcome sets for AF.
Major extracranial bleeds and SEs were included as transient events. These events were associated with cost and QALY decrements; however, they did not affect the health state in which a patient resides.	All models simplify complex patient journeys. The model for this HTA was focused on tracking patients' history of IS and ICH as these events may have sustained impacts of patient QoL and may increase future stroke risk. Nevertheless, this is a limitation.
Dabigatran dose does not reduce as patients age.	Per approach taken in the López-López model.[158,159,226] A reduced dose was explored in sensitivity analysis.
Patients do not stop or change type of OAC after an IS.	ESC guidelines recommend long-term secondary prevention of stroke using OAC in AF patients with IS or TIA.[4] A recent analysis found that changing the type of anticoagulant after an index IS event was not associated with a decreased risk of future IS.[163]
Patients reinstate their initially assigned OAC after an ICH.	ESC guidelines recommend that for AF patients at high risk of IS, re-initiation of OAC should be considered in consultation with a neurologist/stroke specialist after a trauma-related ICH or acute spontaneous ICH, following careful consideration of risk and benefits.[4] A structural sensitivity analysis, in which patients were assumed to stop OAC after an ICH, was included.
Treatment compliance within the hypothetical model cohort (and within the Swiss population, by extension) was aligned with patient compliance in the included RCTs.	Event probabilities were informed by the included RCTs, without further adjustment for differences in compliance between the RCT and Swiss populations. Any differences from the Swiss population are a limitation of the evaluation.
Patients from the RCTs included in the López-López et al 2017 meta-analysis are representative of the NVAF population in Switzerland	Baseline event probabilities came from this meta-analysis.[158,226] Any differences from the Swiss population are a limitation of the evaluation.
An IS or ICH event increases a patient's future risk of stroke, SE and bleed events.	Per the approach taken in the López-López model.[158,159,226]
The effects of prior events (i.e. IS and ICH) on future risk were assumed to be multiplicative.	Per the approach taken in the López-López model.[158,159,226]
IS and ICH events are associated with long-term reductions in QoL.	Per the approach taken in the López-López model.[158,159,226]
For patients with a history of multiple events (i.e. IS and ICH), health state utilities were assumed to be multiplicative	Per the approach taken in the López-López model.[158,159,226]
Mortality rate in the NVAF population relative to the general population does not vary with age.	The approach taken to model age-based mortality increases aligned with the López-López model.[158,159,226]

Abbreviations:
AF: atrial fibrillation; **ESC**: European Society of Cardiology; **HTA**: health technology assessment; ICH: intracranial haemorrhage; **IS**: ischaemic stroke; **MI**: myocardial infarction; **NVAF**: nonvalvular atrial fibrillation; OAC: oral anticoagulant; **PICO**: population, intervention, comparator, outcome; **QALY**: quality-adjusted life year; **QoL**: quality of life; **RCT**: randomised controlled trial; **SE**: systemic embolism; **TIA**: transient ischaemic attack.

17.3 Economic model input appendices

17.3.1 Relative effect of no treatment relative to VKAs

For the structural sensitivity analysis which assumed that OAC would be stopped after an ICH, it was necessary to adjust the risk of clinical events for patients with a history of ICH to reflect the risk of events among patients not receiving oral anticoagulation. Transition probabilities for patients not receiving OAC (i.e. with a history of ICH) were derived using estimates of relative treatment efficacy for no treatment compared to warfarin. These estimates of relative treatment efficacy (see ***Table 126***) were mostly borrowed directly from the *López-López model.*[44,158]

To compute transition probabilities, annual hazards for each clinical event with usual care (i.e. VKAs) were multiplied by the estimates of relative treatment efficacy, then converted into 3-month probabilities.

Table 126 Hazard ratio of clinical events for patients who discontinue oral anticoagulation

Clinical event	No treatment
IS	3.00 (1.84 to 4.83)
SE	19.2 (0.085 to 39.4)
ICH	No data available; assume equal to the HR for bleeds
Clinically-relevant bleed	0.51 (0.205 to 0.95)
All-cause mortality	1.65 (0.58 to 3.57)

Abbreviations:
HR: hazard ratio; **ICH**: intracranial haemorrhage; **IS**: ischaemic stroke; **SE**: systemic embolism.
Notes:
Results are reported as HRs (95% CI) relative to VKAs.

17.3.2 Relative effect of reduced dose DOACs

Table 127 RCT-based estimates of relative treatment effect for reduced dose DOACs

	IS	SE [a]	ICH	Major bleed [b]	Death (all cause)
Dabigatran 110 mg	1.12 (0.90 to 1.40)	0.91 (0.74 to 1.10	0.31 (0.20 to 0.48)	0.81 (0.71 to 0.93)	0.92 (0.81 to 1.04)

Abbreviations:
ICH: intracranial haemorrhage; **IS**: ischaemic stroke; **SE**: systemic embolism.
Notes:
Results are reported as RRs and 95% CIs.
[a] The effect estimate for the combined outcome of stroke or SE was used as a proxy to reflect the relative impact of DOACs on the occurrence of SE in the model.
[b] The relative treatment effect for major/life-threatening bleeding was used to reflect the relative effect of DOACs on the occurrence of extracranial bleed events in the model.

17.3.3 Hospital and inpatient rehabilitation costs for acute events

DRG codes B39A–C and B70A–G were identified as relevant for non-fatal stroke events with more than one day's occupancy, without differentiating between ischaemic and haemorrhagic origins. The mean cost per episode and LOS for each of these DRG codes, and the simple averages across this group of codes, are provided in ***Table 128***.[180]

Table 128 Hospital costs for stroke events (ischaemic or haemorrhagic)

DRG code	Description	Average cost per episode (CHF)	Average LOS (days)
B39A	Complex neurological treatment of an acute stroke lasting more than 72 hours with surgery and extremely severe CC	46,224.25	13.2
B39B	Complex neurological treatment of an acute stroke lasting more than 72 hours with a specific procedure or complex medical intensive care treatment	33,610.85	9.4
B39C	Neurological complex treatment of acute stroke with surgical intervention	27,431.30	8
B70A	Stroke with neurological complex treatment of the acute stroke > 72 hours, with complicating diagnosis or severe motor dysfunction or extremely severe CC	25,279.70	10.9
B70B	Stroke with neurological complex treatment of the acute stroke > 72 hours or neurological complex diagnostics	17,931.60	8
B70C	Stroke with neurological complex treatment of acute stroke < 73 hours, with complicating diagnosis or thrombolysis or severe motor dysfunction	14,794.15	6.5
B70D	Stroke with neurological complex treatment of acute stroke < 73 hours, or with other neurological complex treatment > 72 hours, or extremely severe CC	13,841.75	6.7
B70E	Stroke with other neurological complex treatment of acute stroke < 73 hours or neurological complex diagnostics	12,128.95	6.3
B70F	Stroke, more than one day of occupancy, or thrombolytic therapy complicating the diagnosis or severe motor dysfunction	12,693.90	7.9
B70G	Apoplexy, more than one day of occupancy	9,927.00	6.4
Average (simple)		21,386.35	8.33
Minimum		9,927.00	6.4
Maximum		46,224.25	13.2

Abbreviations:
CC: complications or comorbidities; **CHF**: Swiss francs; **LOS**: length of stay.

DRG codes G67A–D informed the event cost for major/clinically-relevant extracranial bleeds. The mean cost per episode and LOS for each of these DRG codes, and the simple averages across this group of codes, are provided in ***Table 129***.[180]

Table 129 Hospital costs for GI bleed events

DRG code	Description	Average cost per episode (CHF)	Average LOS (days)
G67A	Ulcer disease with GI bleeding, more than one day of occupancy and extremely severe CC	16,525.05	10.7
G67B	Various diseases of the digestive organs or GI bleeding or ulcer disease, with dialysis or extremely severe CC or para-/tetraplegia	10,940.55	6.9
G67C	Various diseases of the digestive organs or GI bleeding or ulcer disease with severe CC or coagulation disorder	9,126.30	6.1
G67D	Various diseases of the digestive organs or GI bleeding or ulcer disease	5,471.00	3.8
Average (simple)		10,515.73	6.9
Min		5,471.00	3.8
Max		16,525.05	10.7

Abbreviations:
CC: complications or comorbidities; **CHF**: Swiss francs; **GI**: gastrointestinal; **LOS**: length of stay.

LOS data for ICD-10 codes I74.XX informed the event cost for SE. Mean LOS data for each ICD-10 codes, and the weighted average across this group of codes, are provided in ***Table 130***.[181]

Table 130 Hospital LOS data for arterial embolism and thrombosis ICD-10 codes

ICD-10 code	Description	Average LOS (days)	Number of cases
I74.0	Embolism and thrombosis of the abdominal aorta	10.7	112
I74.1	Embolism and thrombosis of other and unspecified sections of the aorta	10.9	18
I74.2	Embolism and thrombosis of the arteries of the upper extremities	6.0	132
I74.3	Embolism and thrombosis of the arteries of the lower extremities	9.2	1,079
I74.4	Embolism and thrombosis of limb arteries, unspecified	12.8	12
I74.5	Embolism and thrombosis of the iliac artery	8.2	112
I74.8	Embolism and thrombosis of other arteries	8.1	25
I74.9	Embolism and thrombosis of unspecified artery	4.0	2
Average (weighted)		8.98	Total: 1,492

Abbreviations:
ICD-10: International Classification of Diseases, 10th revision; **LOS**: length of stay.

RCGs TR13A–C informed the daily cost of inpatient rehabilitation following a stroke (of either ischaemic or haemorrhagic origin). Daily costs weights for these RCGs, and the average across the RCG group, are presented in ***Table 131***. The calculated daily costs and costs per episodes derived from these daily cost weights, along with additional sources, are also presented.

Table 131 Daily costs and costs per episode for inpatient rehabilitation after stroke

RCG	Description	Daily Cost Weight	Daily Cost (CHF) [a]	Cost per episode (CHF) [b]
TR13: Neurological Rehabilitation				
TR13A	Complex neurological rehabilitation with complicating diagnosis or with high additional effort	1.348	1,024.48	74,069.90
TR13B	Neurological rehabilitation with complicating diagnosis or with additional effort or with specific treatment	1.114	846.64	61,212.07
TR13C	Neurological Rehabilitation	1.007	765.32	55,332.64
Average (simple)		1.156	878.56	63,519.89

Abbreviations:
CHF: Swiss francs; **RCG**: rehabilitation cost groups.
Notes:
[a] Daily costs weights were multiplied by a based price per day of CHF760.[183]
[b] Daily costs were multiplied by the mean duration of inpatient rehabilitation reported in a Swiss survey of 72.3 days.[185]

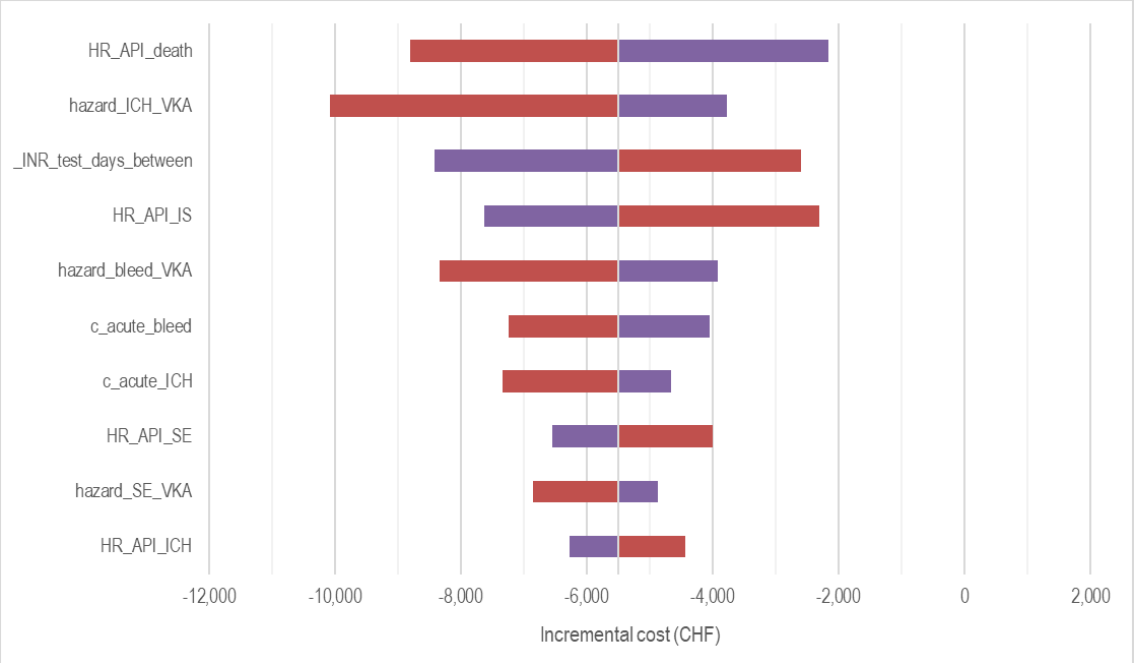
17.4 Economic results appendices

17.4.1 Apixaban vs VKAs: NRSI scenario

17.4.1.1 Univariate sensitivity analysis

Univariate DSAs were used to identify key model drivers of the apixaban vs VKAs NRSI scenario. The top 10 drivers in the incremental cost and incremental QALYs were displayed visually using tornado diagrams (***Figure 53*** and ***Figure 54***).

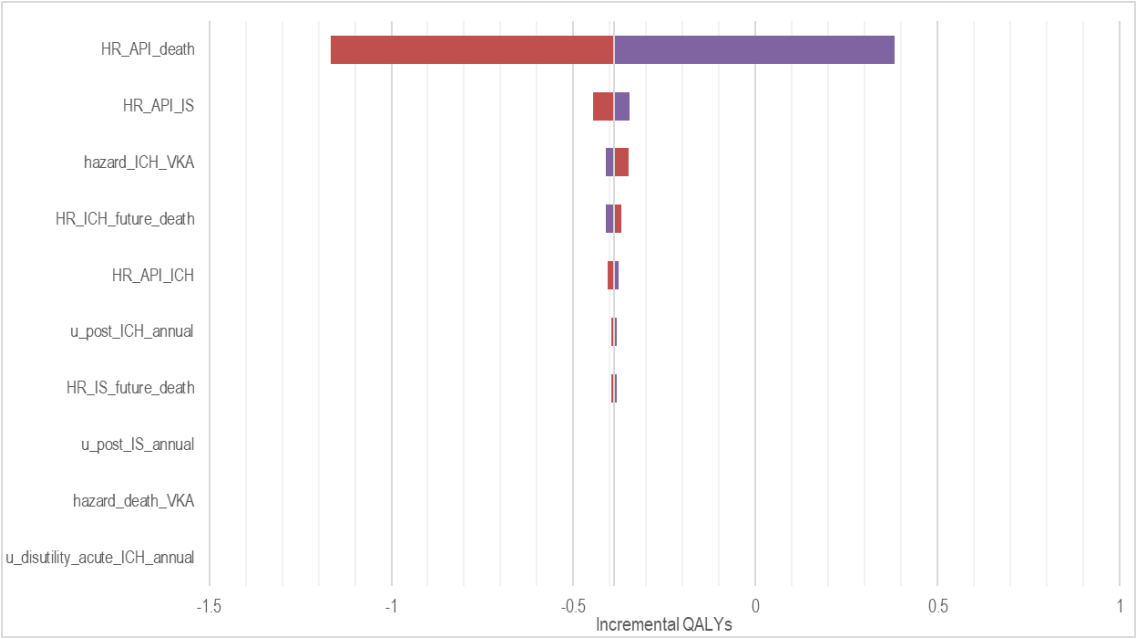
Figure 53 Incremental cost tornado diagram for the apixaban NRSI scenario



Abbreviations:

API: apixaban; **CHF**: Swiss francs; **HR**: hazard ratio; **ICH**: intracranial bleed; **INR**: international normalised ratio; **IS**: ischaemic stroke; **SE**: systemic emoblism; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

Figure 54 Incremental QALYs tornado diagram for the apixaban NRSI scenario

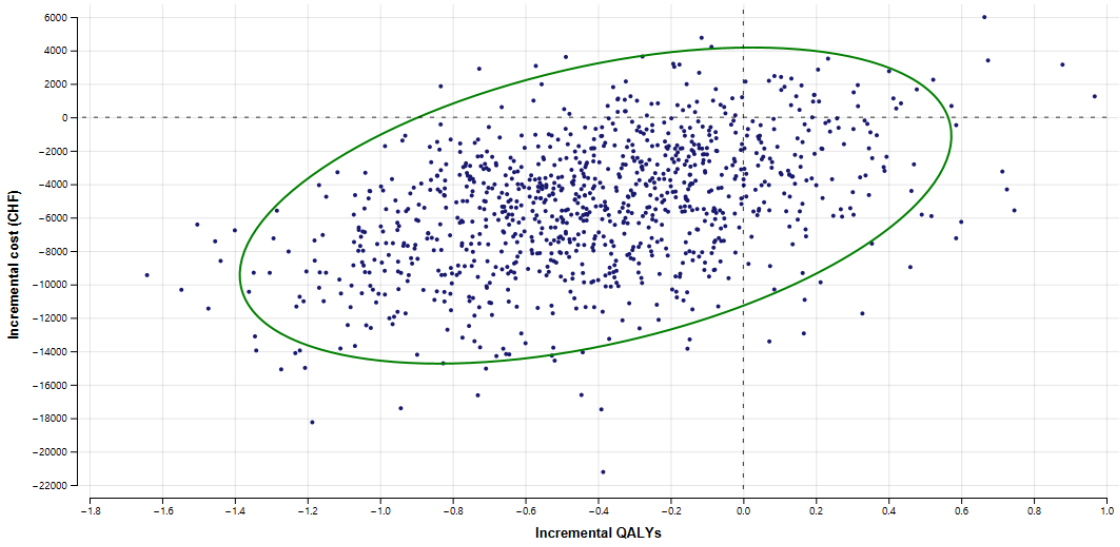


Abbreviations:
API: apixaban; **HR**: hazard ratio; **ICH**: intracranial bleed; **IS**: ischaemic stroke; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

17.4.1.2 Probabilistic sensitivity analysis on the NRSI scenario

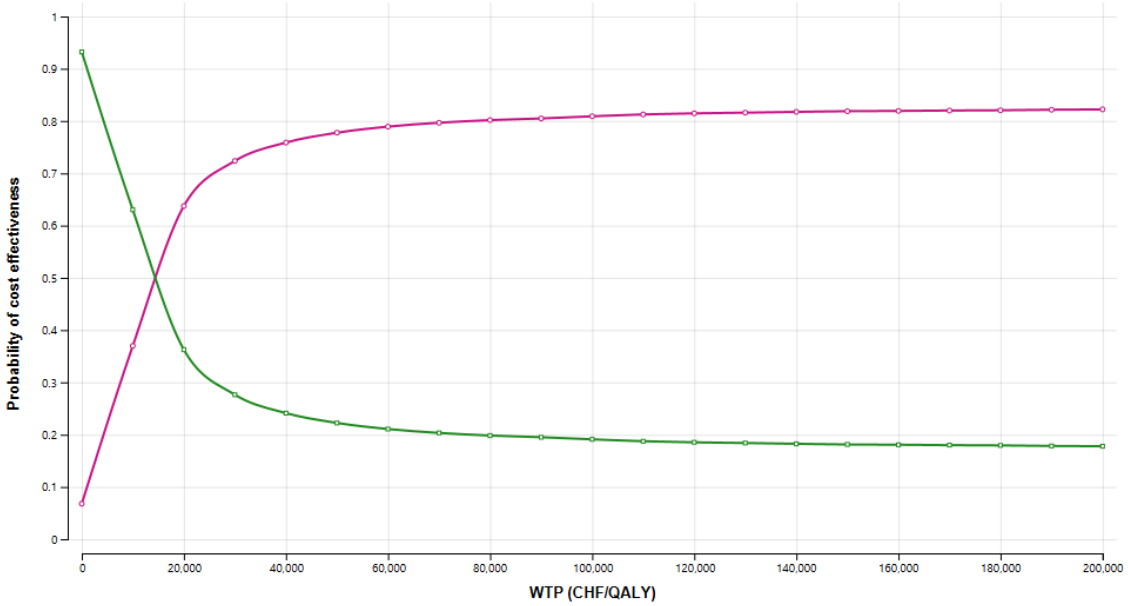
PSA was undertaken to explore the overall certainty of the economic findings from the apixaban vs VKA NRSI scenario. Results are presented as 95% confidence ellipses on the CE plane (***Figure 55***) and as a CEAC (***Figure 56***).

Figure 55 Cost-effect pairs on the CE plane for apixaban vs VKA based on NRSI data



Abbreviations:
CHF: Swiss francs; **QALY**: quality-adjusted life year.

Figure 56 CEAC for apixaban vs VKA based on NRSI data



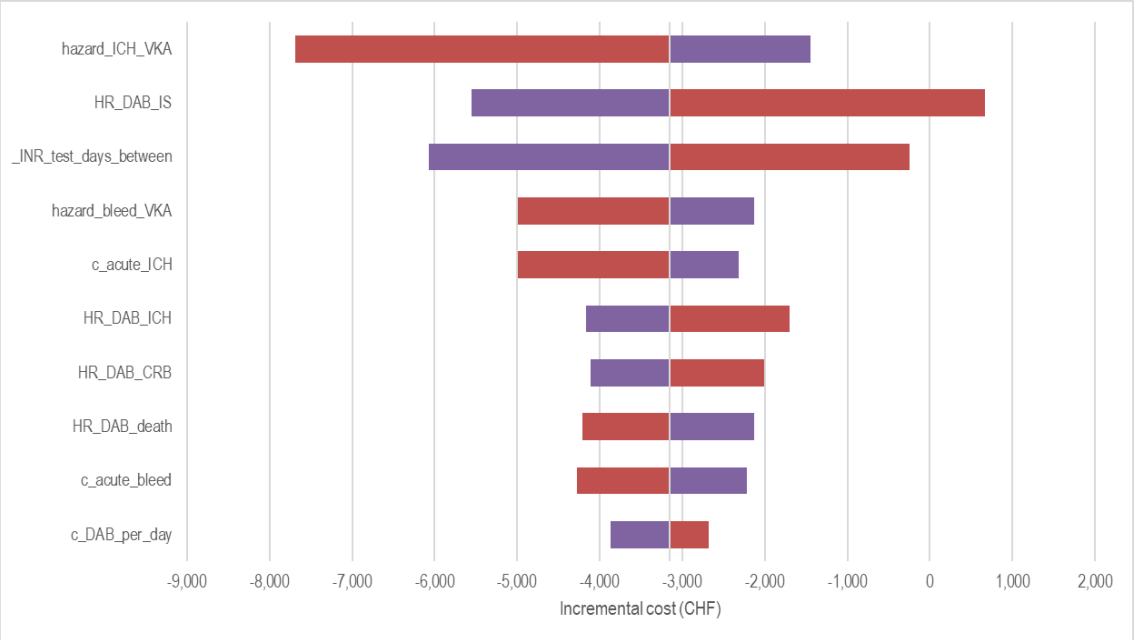
Abbreviations:
CEAC: cost-effectiveness acceptability curve; **CHF**: Swiss francs; **QALY**: quality-adjusted life year; **WTP**: willingness to pay.
Notes:
The green and pink lines represent the probability of cost effectiveness for apixaban and VKA, respectively.

17.4.2 Dabigatran vs VKAs: NRSI scenario

17.4.2.1 Univariate sensitivity analysis

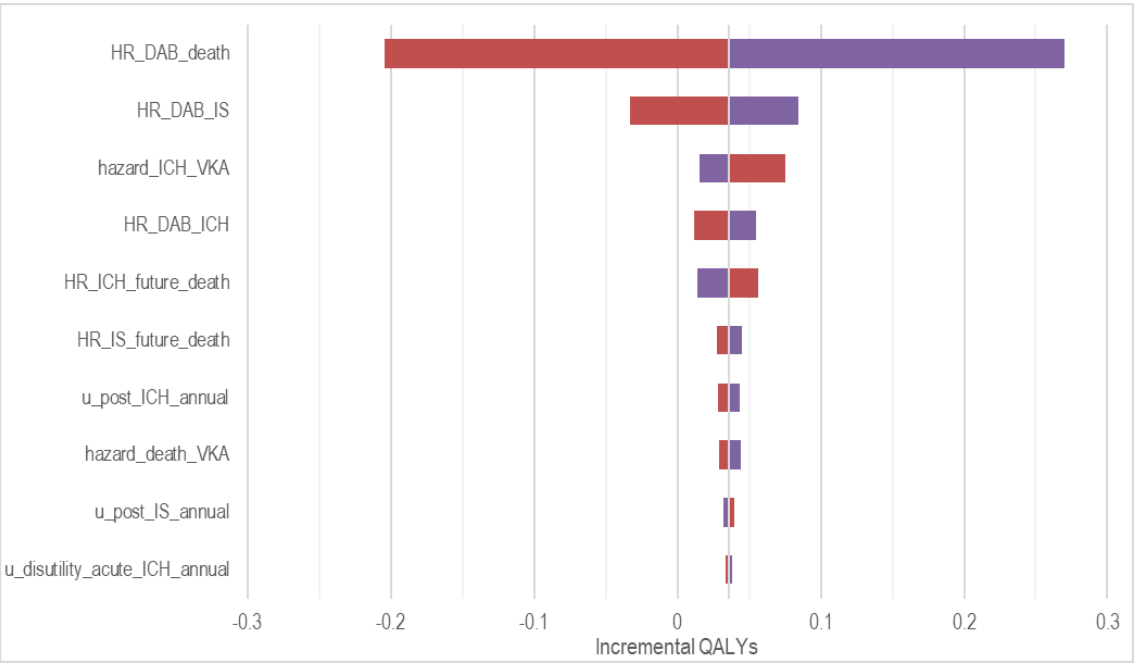
Univariate DSAs were used to identify key model drivers of the dabigatran vs VKAs NRSI scenario. The top 10 drivers of the incremental cost and QALYs were displayed visually using tornado diagrams (***Figure 57*** and ***Figure 58***).

Figure 57 Incremental cost tornado diagram for the dabigatran NRSI scenario



Abbreviations:
CHF: Swiss francs; **DAB**: dabigatran; **HR**: hazard ratio; **ICH**: intracranial haemorrhage; **INR**: international normalised ratio; **IS**: ischaemic stroke; **SE**: systemic embolism; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

Figure 58 Incremental QALYs tornado diagram for the dabigatran NRSI scenario

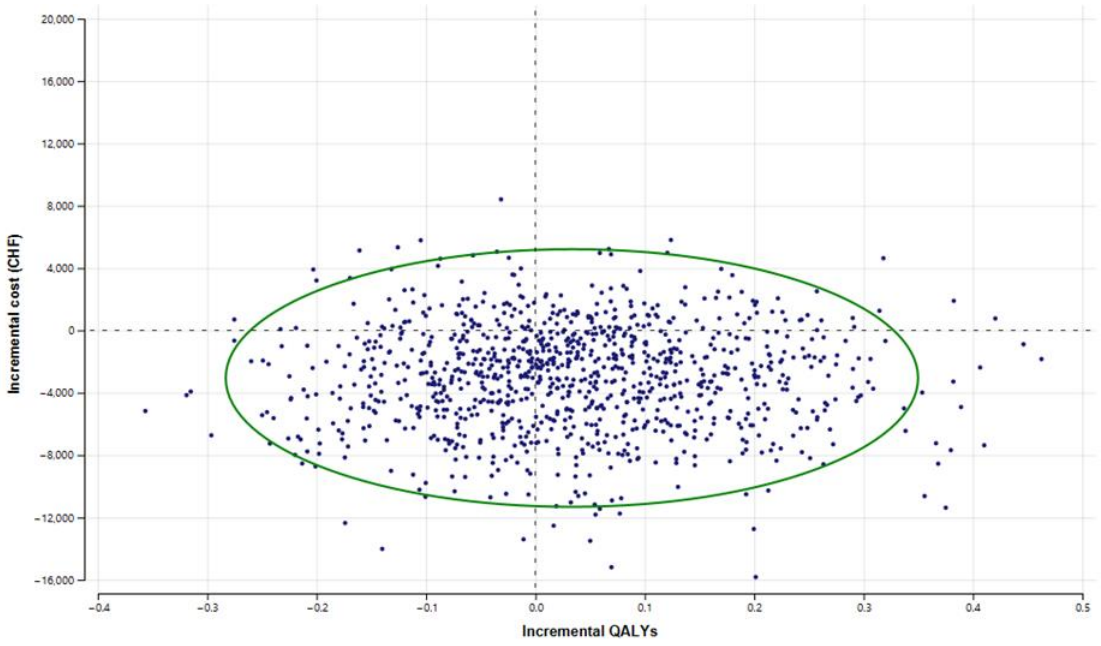


Abbreviations:
DAB: dabigatran; **HR**: hazard ratio; **ICH**: intracranial haemorrhage; **IS**: ischaemic stroke; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

17.4.2.2 Probabilistic sensitivity analysis on the NRSI scenario

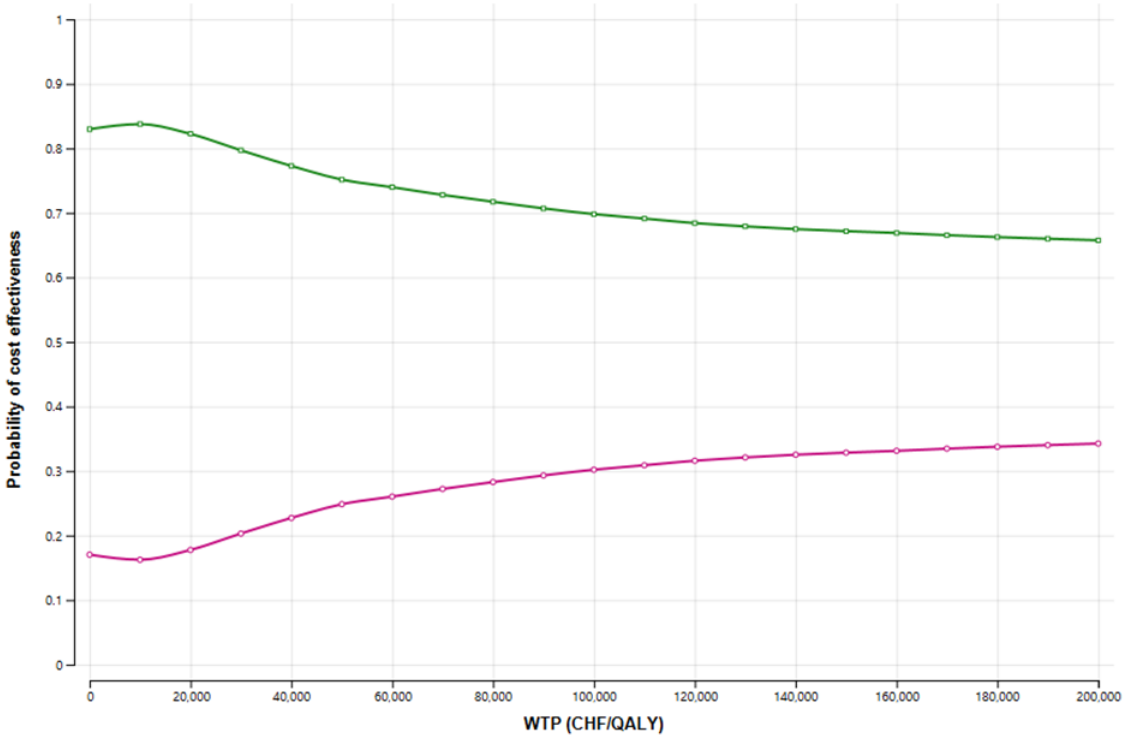
PSA was undertaken to explore the overall certainty of the economic findings from the dabigatran vs VKA NRSI scenario. Results are presented as 95% confidence ellipses on the CE plane (***Figure 59***) and as a CEAC (***Figure 60***).

Figure 59 Cost-effect pairs on the CE plane for dabigatran vs VKA based on NRSI data



Abbreviations:
CE: cost-effectiveness; **CHF**: Swiss francs; **NRSI**: non-randomised studies of interventions; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.

Figure 60 CEAC for dabigatran vs VKA based on NRSI data



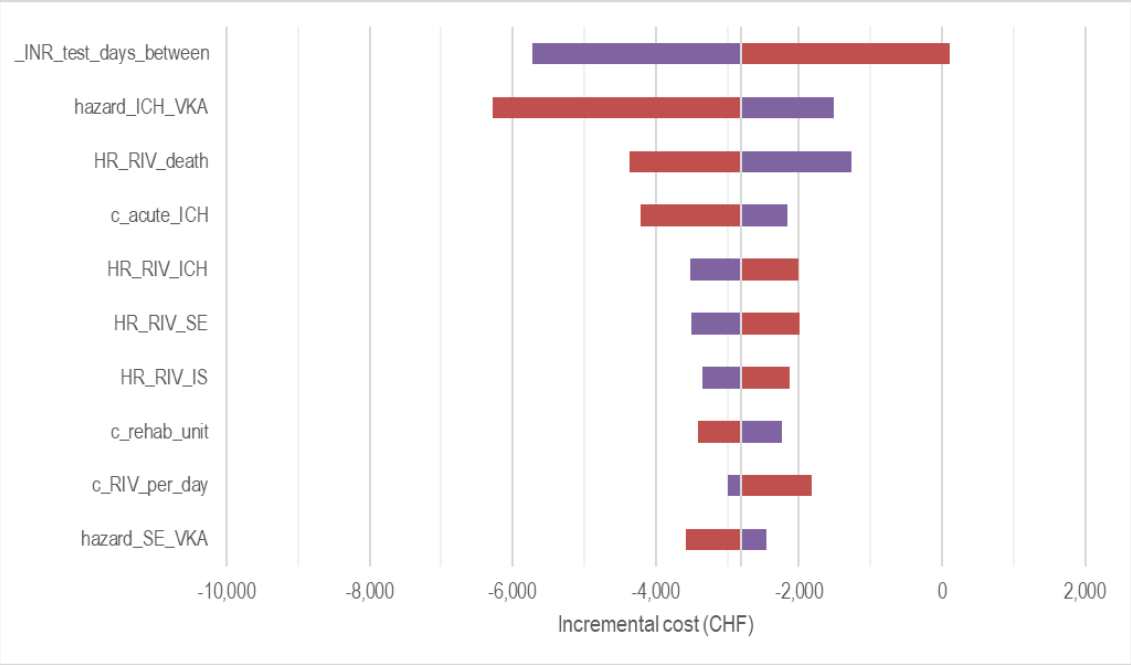
Abbreviations:
CEAC: cost-effectiveness acceptability curve; **CHF**: Swiss francs; **NRSI**: non-randomised studies of interventions; **QALY**: quality-adjusted life year; **WTP**: willingness to pay.
Notes:
The green and pink lines represent the probability of cost effectiveness for dabigatran and VKA, respectively.

17.4.3 Rivaroxaban vs VKAs: NRSI scenario

17.4.3.1 Univariate sensitivity analysis

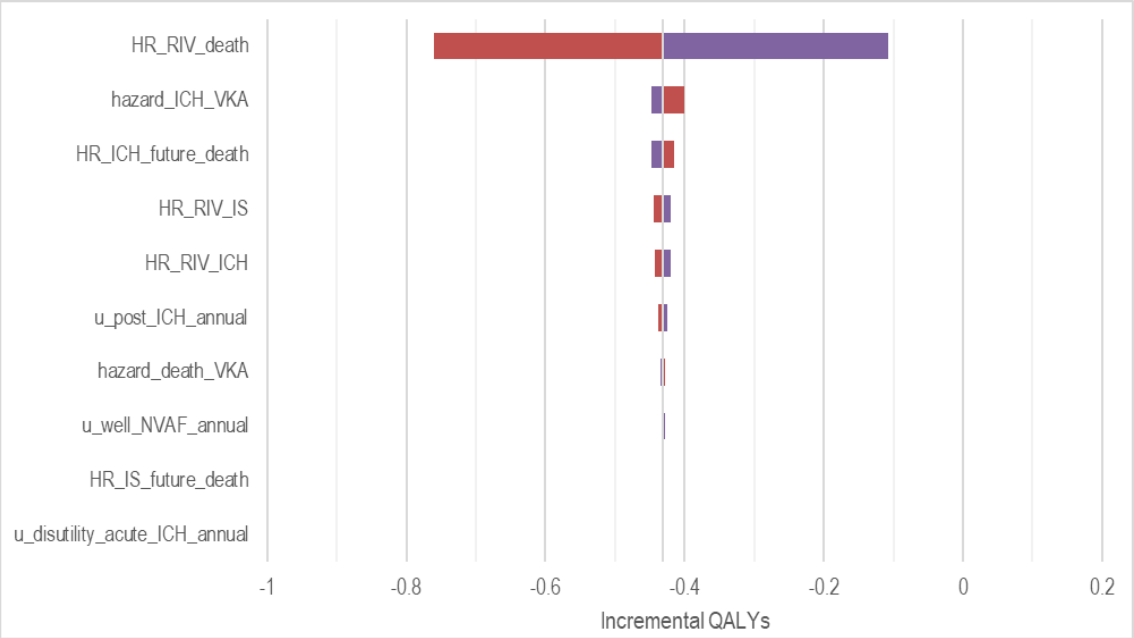
Univariate DSAs were used to identify key model drivers of the rivaroxaban vs VKA NRSI scenario. The impacts of each variable on incremental costs and QALYs were explored. The top 10 drivers were displayed visually using tornado diagrams (***Figure 61*** and ***Figure 62***).

Figure 61 Incremental cost tornado diagram for the rivaroxaban NRSI scenario



Abbreviations:
HR: hazard ratio; **ICH**: intracranial haemorrhage; **INR**: international normalised ratio; **IS**: ischaemic stroke; **RIV**: rivaroxaban; **SE**: systemic embolism; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

Figure 62 Incremental QALYs tornado diagram for the rivaroxaban NRSI scenario

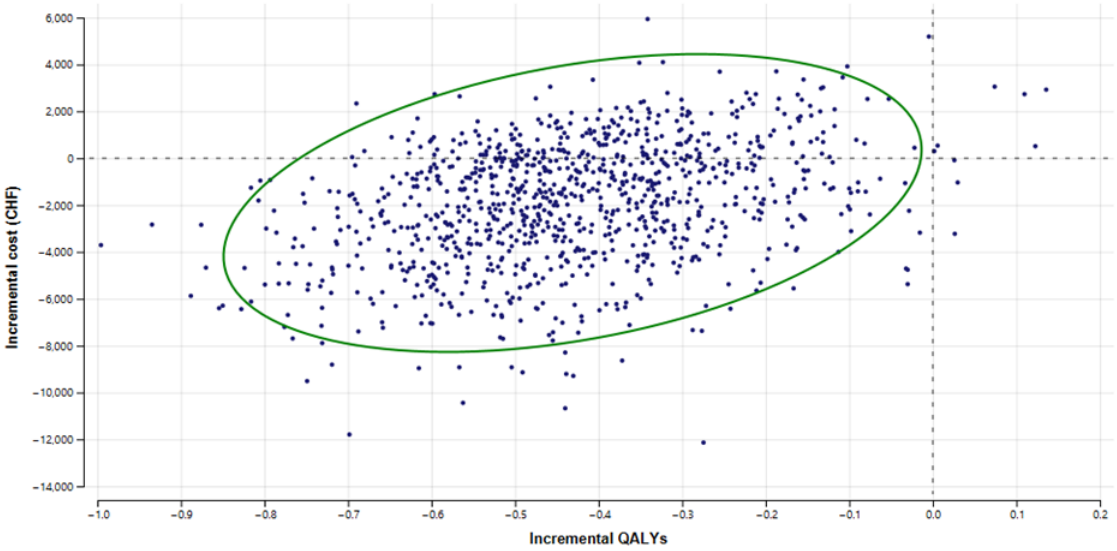


Abbreviations:
HR: hazard ratio; **ICH**: intracranial haemorrhage; **IS**: ischaemic stroke; **NVAF**: nonvalvular atrial fibrillation; **RIV**: rivaroxaban; **SE**: systemic embolism; **VKA**: vitamin K antagonist.
Notes:
The purple and red bars represent the lower and upper bounds of each parameter's uncertainty range, respectively.

17.4.3.2 Probabilistic sensitivity analysis on the NRSI scenario

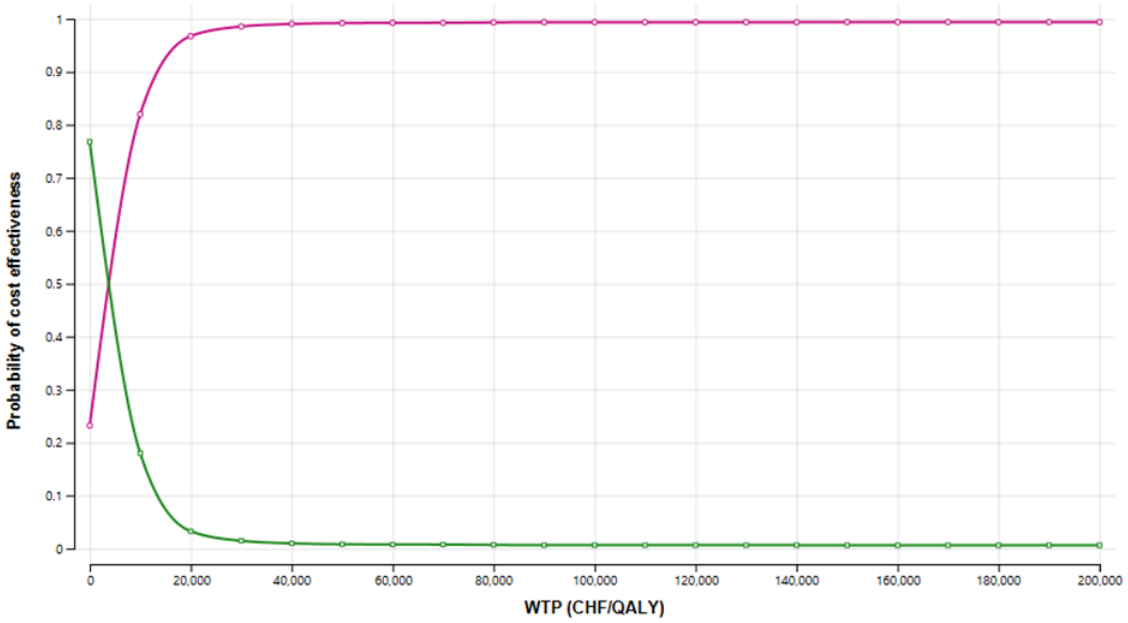
PSA was undertaken to explore the overall certainty of the economic findings from the rivaroxaban vs VKA NRSI scenario. Results are presented as 95% confidence ellipses on the CE plane (***Figure 63***) and as a CEAC (***Figure 64***).

Figure 63 Cost-effect pairs on the CE plane for rivaroxaban vs VKA based on NRSI data



Abbreviations:
CE: cost-effectiveness; **CHF**: Swiss francs; **NRSI**: non-randomised studies of interventions; **QALY**: quality-adjusted life year; **VKA**: vitamin K antagonist.

Figure 64 CEAC for rivaroxaban vs VKA based on NRSI data



Abbreviations:
CEAC: cost-effectiveness acceptability curve; **CHF**: Swiss francs; **NRSI**: non-randomised studies of interventions; **QALY**: quality-adjusted life year; **WTP**: willingness to pay.
Notes:
The green and pink lines represent the probability of cost effectiveness for rivaroxaban and VKA, respectively

17.5 Results from other economic studies

Table 132 Summary of results from a selection of economic evaluation studies

Study ID	Interventions considered	Perspective, time horizon, discount	ICER	Key model drivers	PSA results	Comments
Austria						
Walter et al 2021[100]	API vs VKA	Payer's perspective Lifetime horizon 5% p.a. for costs and effects	€12,743/QALY	API remained CE in all but one DSA – the upper bound of the relative effect estimate for API on mortality	At WTP of €28,000, API had a 76.4% probability of being CE	Other DOACs were also included; however they were compared to API, not VKA. Adaptation of the *López-López model*.
France						
Chevalier et al 2014[108]	DAB vs VKA	Payer's perspective Lifetime horizon 4% for costs and effects	€15,838 (vs trial-like VKA); €7,474 (vs real-world VKA)	DAB vs trial-like VKA most sensitive to RR of IS and time horizon of the model.	At WTP of €24,000/€36,000, DAB had 71% and 100% probabilities of being CE vs trial-like and real-world VKA.	The real-world VKA scenario is not clearly defined. Adaptation of the *Sorensen model*.
De Pouvourville et al 2020[109]	DAB vs VKA	Payer's perspective Lifetime horizon 4% for costs and effects	RCT: €8,077 (€13,116 for 100 mg dose); Real-world: DAB dominant (for both 150 mg and 100 mg doses).	NR	DAB (150 mg) had >50% probability of being CE beyond WTPs of €10,000 and €6,000 for the RCT and real-world analysis, respectively. DAB (100 mg) had >50% probability of being CE beyond WTPs of €16,000 and at any WTP, respectively.	Updating the model with real-world effect estimates and monitoring and event costs improved the CE of DAB. Adaptation of the *Sorensen model*.

Study ID	Interventions considered	Perspective, time horizon, discount	ICER	Key model drivers	PSA results	Comments
Germany						
Krejczy et al 2014[113]	API vs VKA DAB vs VKA RIV vs VKA	Payer's perspective 20-year time horizon 5% p.a. costs & effects	€57,245 (API), €163,184 (DAB 150 mg), €294,349 (DAB 100 mg), and €133,926 (RIV).	Drivers included drug costs, health state utilities for each drug, risks for stroke and major/life-threatening bleeding for the DOACs and for VKAs.	The probability of API, DAB (150 mg), DAB (100 mg) and RIV reached >50% at WTPs of €60,500, €175,500, €278,000, and €136,500, respectively.	
Krejczy et al 2015[114]	EDO vs VKA	Payer's perspective 20-year time horizon 5% p.a. costs & effects	€52,000 (EDO 60 mg), €69,600 (EDO 30 mg)	Drivers included the cost of EDO, health state utilities, the treatment of IS and of major bleeds and ICH.	EDO (60 mg) and EDO (30 mg) reached >50% probability of being CE at WTPs of €52,000 and €67,000, respectively.	Results for API, DAB and RIV are also presented; however, these are referenced as coming from Krejczy 2014,[113] so have not been extracted here. Adaptation of Krejczy 2014 [113]
Mensch et al 2015[112]	RIV vs VKA	Payer's perspective Lifetime horizon (35 years) 3% p.a. costs & effects	€15,207	The most influential variables included the time horizon, daily cost of RIV and relative effect of RIV on ICH.	At WTPs of €15,000 and €25,000, RIV had 73% and 99% probabilities, respectively, of being CE	
Italy						
Lorenzoni et al 2021[153]	API vs VKA DAB vs VKA RIV vs VKA	Payer's perspective Lifetime horizon 3.5% p.a. costs & effects	All DOACs dominated VKA	Relative effect estimates of API and DAB on mortality. API, DAB and RIV drug costs. ICERs remained negative (i.e. DOACs dominant) in all DSAs.	API: majority of iterations in the second quadrant (i.e. API dominant); % not provided. DAB & RIV: «high degree of uncertainty»; % not provided.	Adaptation of the *López-López model*.

Study ID	Interventions considered	Perspective, time horizon, discount	ICER	Key model drivers	PSA results	Comments
Ravasio et al 2014[121]	API vs VKA DAB vs VKA RIV vs VKA	Payer's perspective Lifetime horizon 3% p.a. costs & effects	€7,586 (API), €6,795 (DAB), and €24,967 (RIV) [a]	Key drivers included the relative risk of IS and the time horizon.	At a WTP of €40,000, DAB had a 100% probability of being CE (according to the text). Probability of CE for other pairwise DOAC vs VKA comparison not presented.	Adaptation of the *Sorensen model*.
Rognoni et al 2014[119]	API vs VKA DAB vs VKA RIV vs VKA	Payer's perspective Lifetime horizon 3.5% p.a. costs & effects	€7,942 (API), €8,099 (DAB), and €16,162 (RIV)	Time horizon, daily cost of DOACs and RR of IS (DOACs vs VKA). $CHADS_2$ ≤1: €9,631 (API), €7,320 (DAB); $CHADS_2$ =2: €9,660 (API), €7,609 (DAB), €20,089 (RIV); $CHADS_2$ ≥3: €4,723 (API), €12,029 (DAB), and €13,063 (RIV).	At a WTP of €25,000, API, DAB and RIV had probabilities of 94.8%, 96.2% and 71,1%, respectively, of being CE.	
Rognoni et al 2015[120]	EDO vs VKA	Payer's perspective Lifetime horizon 3.5% p.a. costs & effects	€7,713	Time horizon, health state utilities for the well with NVAF on EDO/on VKA states. $CHADS_2$ ≤3: €9,438 $CHADS_2$ >3: €5,363	At a WTP of €25,000, EDO had a 92.3% probability of being CE.	Adaptation of Rognoni 2014 [119]
Switzerland						
Pletscher et al 2013[140]	DAB vs VKA	Payer's perspective Lifetime horizon 2% p.a. costs & effects	€9,702 (DAB 150 mg), €25,108 (DAB 100 mg), and €10,215 (sequential dosing).	DAB remained CE under all scenarios tested.	At WTP of CHF100,000, DAB 150 mg, 100 mg, and sequential dosing options had 99.0%, 95.6% and 99.6% probabilities of being CE, respectively.	Adaptation of the *Sorensen model*.

Study ID	Interventions considered	Perspective, time horizon, discount	ICER	Key model drivers	PSA results	Comments
UK						
López-López et al 2017[44,158,159]	API vs VKA DAB vs VKA EDO vs VKA RIV vs VKA	Payer's perspective Lifetime horizon 3.5% p.a. costs & effects	Expected INB at WTPs of £20,000 and £30,000 were positive for all DOACs vs VKA [b] API, DAB, EDO dominated VKA. RIV: £1,480.70 [c]	Authors suggested the following as key drivers: The lower rates of MI, ICH and other CRB with API (DAB also had low rates of ICH, higher rates of MI offset the benefit) The high cost and disutility of ICH.	Iterations on the CE plane are presented but no probabilities are provided re: pairwise DOAC vs VKA comparisons.	The aim of the study was to evaluate the most CE first-line OAC for the prevention of IS in patients with AF. Therefore, efficiency frontier analysis was employed.
NICE 2021[58]	API vs VKA DAB vs VKA EDO vs VKA RIV vs VKA	Payer's perspective Lifetime horizon 3.5% p.a. costs & effects	Expected INB at WTPs of £20,000 were positive for all DOACs vs VKA [d] API, DAB, EDO dominated VKA. RIV: £4,332.54 [e]	The same key drivers were reported as found for the original *López-López model*. Authors added that DAB reduced stroke risk more than API, influencing CE outcomes as baseline stroke risk (CHA_2DS_2-VASc) increased.	Probabilities for a frontier analysis are presented, but not re: pairwise DOAC vs VKA comparisons.	Adaptation of the *López-López model*. Main changes comprised: scenario analyses on age, gender and stroke risk, updating all unit costs to 2019 and including costs of available reversal agents.

Abbreviations:
AF: atrial fibrillation; **API**: apixaban; **CE**: cost effective; **CRB**: clinically-relevant bleed; **DAB**: dabigatran; **DOAC**: direct oral anticoagulant; **DSA**: deterministic sensitivity analysis; **ECH**: extracranial haemorrhage; **EDO**: edoxaban; **ICH**: intracranial haemorrhage; **INB**: incremental net benefit; **IS**: ischaemic stroke; **MI**: myocardial infarction; **NICE**: National Institute for Health and Care Excellence; **OAC**: oral anticoagulant; **p.a.**: per annum; **QALY**: quality-adjusted life year; **RCT**: randomised controlled trial; **RIV**: rivaroxaban; **RR**: relative risk; **VKA**: vitamin K antagonist; **WTP**: willingness-to-pay.
Notes:
[a] DAB was used as the reference drug in the publication; ICERs for API and RIV relative to VKAs were derived using the reported expected per patient costs and QALYs under each strategy;
[b] Expected incremental net monetary benefits (95% confidence intervals) at willingness-to-pays of £20,000 and £30,000 for each DOAC vs VKA: API: £7,533 (490 to 18,228) and £10,760 (576 to 25,861), respectively; DAB: £6,365 (-168 to 17,039) and £8,871 (-597 to 23,402), respectively; EDO: £5,212 (-894 to 14,826) and £7,601 (-1,556 to 20,987), respectively; RIV: £5,279 (-1,097 to 15,180) and £8,130 (-1,399 to 22,819), respectively.
[c] ICER results were not reported in the publications; they have been derived using the reported mean values for the expected incremental costs and QALYs for each DOAC relative to VKA.
[d] Expected incremental net monetary benefits (95% confidence intervals) at a willingness-to-pay of £20,000 for each DOAC vs VKA: API: £15,259 (5,411 to 26,430); DAB: £12,845 (-97 to 25,554); EDO: £10,426 (-1,056 to 20,837); RIV: £10,804 (-1,907 to 23,370).
[e] ICER results were not reported in the publications; they have been derived using the reported mean values for the expected costs and QALYs for each DOAC and VKA.

17.6 Budget impact appendices

17.6.1 Total OAC drug cost for patients with AF, alternate calculation for 2021

As a validation exercise, total payer cost of each OAC in 2021 (as reported by © COGE GmbH. Tarifpool. © SASIS AG sales data) were multiplied by the proportion of prescriptions for that OAC written for patients with AF (as informed by IQVIA survey data).[178] This calculation, shown in ***Table 133***, provided an alternate estimate of the total payer cost for OACs for patients with AF for the year 2021.

Table 133 Total payer costs for OACs in the treatment of AF for 2021, alternate estimate

	Total cost, 2021 (CHF)[a]	% Due to AF [b]	Estimated cost due to AF, 2021 (CHF)
Apixaban	64,218,242	62.9%	40,388,578
Dabigatran	4,549,003	67.4%	3,065,470
Edoxaban	16,751,138	78.7%	13,187,960
Rivaroxaban [c]	152,319,885	50.1%	76,355,839
VKAs	2,623,038	43.0%	1,128,553
Total	240,461,305		134,126,400

Abbreviations:
AF: atrial fibrillation; **CHF**: Swiss francs; **OAC**: oral anticoagulant; **VKA**: vitamin K antagonist.
Notes:
[a] Sourced from © COGE GmbH Tarifpool. © SASIS AG sales data for the year 2021.
[b] Reflects the average annual number of prescriptions written for patients with atrial fibrillation or atrial flutter (i.e. ICD-10 code I48.XX) reported in the IQVIA survey for the period April 2019 to March 2022.[178]
[c] Excluding Xarelto vascular.

18 Appendix E: Evidence table for the ethical, legal, social and organisational domains

Table 134 Characteristics of included studies for legal, social, ethical and organisational issues

Study; country	Study design	Study aim	Key themes
Abdou et al 2016 [194]	Narrative review	Barriers & predictors of non-adherence (VKA); adherence & persistence with DOAC; measures to improve adherence	*Patient factors*: age, gender, comorbidities, other medical conditions, socioeconomic status, perceptions of risks/benefits *Healthcare provider factors*: knowledge deficits with guidelines *Medication factors:* dosing complexity, drug maintenance
Amin et al 2016 [207]	Narrative review	Importance of adherence and persistence with direct OAC therapy	*Patient factors*: demographic/psychosocial characteristics, patient-prescriber relationship, health literacy, knowledge level *Medication factors:* duration, side-effects, storage; treatment complexity *Healthcare system factors:* accessibility, no of prescriptions filled *Socioeconomic factors:* cost and income, social support
Bertozzo et al 2016 [201]	Design: cohort Sample size: 798	Reasons for warfarin discontinuation	*Patient factors:* age, vascular disease, INR level, bleeding events *Healthcare provider:* frailty/low life expectancy, bleeding, logistic issues, low compliance, other medications
Clarkesmith et al 2017 [208]	Design: systematic review Search dates/strategy: Y Review registration: Y Number of studies: 11	Educational and behavioural interventions for OAC therapy	*Patient factors:* INR levels within therapeutic target range
Dittrich et al 2021 [202]	Narrative review	Challenges of treatment adherence with DOAC therapy	*Patient factors*: forgetfulness, psychiatric disorders, bleeding fears *Healthcare provider factors:* clinical consultations, cost of care *Medication factors*: cost, drug maintenance & restrictions
Farihna et al 2022 [195]	Design: structured review Database: PubMed Search dates/strategy: Y	Factors influencing patient adherence and persistence to NOAC therapy	*Patient-factors:* age, ethnicity, culture, comorbidities, cognition, disability, frailty, awareness of risks/harms, burden of treatment *Healthcare provider factors*: guideline knowledge, expertise in managing bleeds, assessing patient risks/benefits & quality of life *Healthcare system factors:* work setting, cost of care

Study; country	Study design	Study aim	Key themes
Le-Ching et al 2019 [196]	Design: cross sectional Sample size: 208 patients	Quality of life and treatment satisfaction in patients receiving long-term OAC therapy	*Patient factors*: knowledge/understanding; impact of therapy on daily living; satisfaction levels; awareness of risks/benefits.
Llorca et al 2021 [205]	Design: cross sectional Sample size: 60,978	Assessment of gender-based and socioeconomic factors in the prescription of DOAC	*Patient factors*: age, female and living in rural/deprived urban areas contribute to various DOAC prescription patterns
Mas Dalmau et al 2017 [197]	Design: systematic review Search dates/strategy: Y Review registration: N Number of studies: 9	Patient and physician perceptions and attitudes about barriers and facilitators of VKA use	*Patient factors:* knowledge/understanding/satisfaction with OAC *Healthcare provider factors*: information to reinforce OAC use; balance of risks/benefits; role in decision-making and therapy management
O'Neal et al 2018 [211]	Design: cohort Sample size: 223,891	Influence of sociodemographic factors and provider speciality on prescription fill patterns	*Patient factors*: engagement with healthcare providers influenced by race, sex and education *Medication factors*: value of medication according to risk attributes
Osasu et al 2021 [203]	Design: systematic review Search dates/strategy: Y Review registration: N Number of studies: 34	Patient and clinician perceptions of safety and use of OAC	*Patient factors*: age, comorbidities; confidence & experience; patient support & adherence; health & medication beliefs *Healthcare provider factors*: confidence and experience; *Medication factors:* drug safety, poor understanding
Pandya et al 2017 [212]	Design: structured review Search date/strategy: Y Number of studies: 48	Factors underpinning patient acceptance and decision to use OAC therapy	*Patient factors:* medical condition *Medication factors*: drug adjustment, dosing, interactions; maintenance, restrictions *Socioeconomic factors:* financial burden, medication costs *Healthcare system factors:* patient expectations/satisfaction; type of setting (hospital, anticoagulation clinics)
Raparelli et al 2017 [206]	Narrative review	Adherence and persistence for OAC therapy in NVAF patients	*Patient factors*: demographics, comorbidities, other medications *Healthcare provider factors*: knowledge (risk); patient adherence
Reverdin et al 2011 [214]	Design: observational study Sample size: 35	Report on the safety, efficacy and advantages of INR self testing	*Healthcare system factors:* type of setting (at home testing)
Rolls et al 2017 [204]	Design: cross sectional Sample size: 48	Relationship between OAC knowledge, health literacy and self-reported adherence	*Patient factors:* education adherence, knowledge, health literacy and quality of life

Study; country	Study design	Study aim	Key themes
Salmasi et al 2020 [54]	Design: systematic review Search dates/strategy: Y Review registration: N Number of studies: 30	Adherence to OAC therapy among AF patients	*Patient factors:* age, gender, medical condition, cognitive impairment, comorbidities, functional ability *Medication factors*: dosing, other medications, risk of bleeding *Socioeconomic factors*: geographical areas
Shafrin et al 2016 [198]	Design: cross sectional Sample size: 401	Patient and physician preferences for OAC therapy	*Medication factors*: value of medication use according to risk attributes of stroke, major bleed, convenience, dosing frequency, willingness to pay
Song et al 2022 [209]	Design: systematic review Search dates/strategy: Y Review registration: N Number of studies: 10	Effect of decision aids on shared decision-making and health outcomes regarding OAC	*Patient factors*: Decision aids associated with reduced decisional conflict, improved knowledge and OAC uptake
van Til et al 2020 [213]	Design: cross sectional Sample size: 508	Assess for differences in patient preference for OAC therapy	*Medication factors*: Attributes of convenience – INR monitoring, dosing regimen, intake frequency, pill type, interactions with food and/or drugs, need for bridging antidote, distance to practitioner
Wilke et al 2017 [199]	Design: structured review Search dates/strategy: Y Number of studies: 27	Patient preference for OAC treatment	*Patient factors:* risk/benefit ratio, medication preference % monitoring
Woo et al 2019 [200]	Design: qualitative Sample size: 63	Physician level of knowledge in AF management, barriers to prescribing OAC and strategies to optimise AF management	*Healthcare provider factors:* knowledge level of stroke-risk assessment/estimate, OAC benefits *Medication factors:* OAC prescribing practices

Abbreviations:
AF: atrial fibrillation; **CPG:** clinical practice guideline; **DOAC**: direct oral anticoagulant; **INR**: international normalised ratio; **N**: no; **NOAC**: novel oral anticoagulant; **NVAF**: non-valvular atrial fibrillation; **OAC**: oral anticoagulation; **VKA**: vitamin K antagonist; **Y**: Yes.

19 Appendix F: Recommendations from clinical practice guidelines

Table 135 Recommendations from clinical guidelines regarding oral anticoagulants

Author; country	Recommendation	Strength of recommendation [a, b]
American Heart Association/American College of Cardiology/Heart Rhythm Society 2019 [8] USA	1. For patients with AF and an elevated CHA_2DS_2-VASc score of ≥2 in men or ≥3 in women, oral anticoagulants are recommended. Options include: Warfarin Dabigatran Rivaroxaban Apixaban Edoxaban	1. Strong (1) Grade A for all anticoagulants, apart from edoxaban (moderate)
	2. DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in DOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve).	2. Strong (1) Grade A
	3. Among patients treated with warfarin, the INR should be determined at least weekly during initiation of anticoagulant therapy and at least monthly when anticoagulation (INR in range) is stable.	3. Strong (1) Grade A
	5. For patients with AF who have mechanical heart valves, warfarin is recommended.	5. Strong (1) Grade A
	7. Renal function and hepatic function should be evaluated before initiation of a DOAC and should be re-evaluated at least annually	7. Strong (1) Grade B
	8. In patients with AF, anticoagulant therapy should be individualised on the basis of shared decision-making after discussion of the absolute risks and relative risks of stroke and bleeding, as well as the patient's values and preferences.	8. Strong (1) Grade B
	10. Re-evaluation of the need for and choice of anticoagulant therapy at periodic intervals is recommended to reassess stroke and bleeding risks.	10. Strong (1) Grade B
	11. For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) who are unable to maintain a therapeutic INR level with warfarin, use of a DOAC is recommended.	11. Strong (1) Grade C
	13. For patients with AF who have a CHA_2DS_2- VASc score of ≥2 in men or ≥3 in women and who have end-stage CKD (CrCl<15 ml/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation.	13. Conditional (2) Grade A
	14. For patients with AF (except with moderate-to- severe mitral stenosis or a mechanical heart valve) and moderate-to-severe CKD (serum creatinine ≥1.5 mg/dL [apixaban], CrCl 15 to 30 ml/min [dabigatran], CrCl ≤50 ml/min [rivaroxaban], or CrCl 15 to 50 ml/min [edoxaban]) with an elevated CHA_2DS_2-VASc score, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (eg, dabigatran, rivaroxaban, apixaban or edoxaban).	14. Conditional (2) Grade A
	16. In patients with AF and end-stage CKD or on dialysis, the direct thrombin inhibitor dabigatran or the factor Xa inhibitors rivaroxaban or edoxaban are not recommended because of the lack of evidence from clinical trials that benefit exceeds risk.	16. Conditional (2) Grade C
	17. The direct thrombin inhibitor dabigatran should not be used in patients with AF and a mechanical heart valve.	17. Strong (1) Grade A

CHEST guideline and expert panel report 2018 [218] Endorsed by the AF Association, American College of Clinical Pharmacy, Arrhythmia Alliance and StopAfib.org No applicable jurisdiction	2. For patients with AF, including those with paroxysmal AF, we recommend stroke prevention should be offered to those AF patients with one or more non-sex CHA2DS2-VASc stroke risk factors (score of ≥1 in a male or ≥2 in a female). 5. In VKA-treated patients, we suggest the use of the HAS-BLED score for bleeding risk assessment. 7. In patients with AF who are eligible for OAC, we recommend DOACs over VKA. 8. In patients on VKAs with consistently low time in INR therapeutic range (e.g. TTR <65%), we recommend considering interventions to improve TTR or switching to DOACs. 9. In patients with prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of bleeding, we suggest using apixaban, edoxaban, or dabigatran 110 mg (where available) as all demonstrate significantly less major/life-threatening bleeding compared with warfarin. 10. For patients with non-valvular AF, when VKAs are used, we suggest the target should be INR 2.0–3.0, with attention to individual TTR, ideally ≥70%. 11. For patients with AF, we suggest the SAMe-TT_2R_2 score to aid decision-making to help identify patients likely to do well on VKA. 31. For patients with AF and stable coronary artery disease (e.g. no acute coronary syndrome within the previous year) and who choose OAC, we suggest OAC with either an DOAC or adjusted dose VKA therapy alone (target INR range, 2.0–3.0) rather than the combination of OAC and aspirin. 34. In AF patients with acute ischemic stroke, we suggest that very early anticoagulation (<48 h) using heparinoids or VKA should not be used. 37. In patients with AF and high ischemic stroke risk, we suggest anticoagulation with a DOAC after acute spontaneous ICH (which includes subdural, subarachnoid and intracerebral haemorrhages) after careful consideration of the risks and benefits. 45. For women receiving OAC for prevention of stroke/TE in AF who become pregnant, we suggest discontinuation of OAC with a VKA between weeks 6 and 12 and replacement by LMWH twice daily (with dose adjustment according to weight and target anti-Xa level 4–6 h post-dose 0.8–1.2 U/ml), especially in patients with a warfarin dose required of >5 mg/day (or phenprocoumon >3 mg/day or acenocoumarol >2 mg/day). OAC should then be discontinued and replaced by adjusted-dose LMWH (target anti-Xa level 4–6 h post-dose 0.8–1.2 U/ml) in the 36th week of gestation. 46. For women on treatment with long-term VKAs who are attempting pregnancy and are candidates for LMWH substitution, we suggest performing frequent pregnancy tests and use LMWH instead of VKA when pregnancy is achieved rather than switching to LMWH while attempting pregnancy. 47. For pregnant women, we suggest avoiding the use of DOACs. 48. For lactating women using warfarin, acenocoumarol or UFH who wish to breastfeed, we suggest continuing the use of warfarin,	2. Strong recommendation, moderate quality evidence 5. Weak recommendation, low quality evidence 7. Strong recommendation, moderate quality evidence 8. Strong recommendation, moderate quality evidence 9. Weak recommendation, very low-quality evidence 10. Ungraded consensus-based statement 11. Ungraded consensus-based statement 31. Weak recommendation, low quality evidence 34. Ungraded consensus-based statement 37. Ungraded consensus-based statement 45. Ungraded consensus-based statement 46. Ungraded consensus-based statement 47. Ungraded consensus-based statement 48. Ungraded

	acenocoumarol, LMWH or UFH. 49. For breastfeeding women, we suggest alternative anticoagulants rather than DOACs. 52. In severe non-dialysis CKD (Stage IV CrCl 15–30 ml/min), we suggest using VKAs and selected DOACs (rivaroxaban 15 mg once daily, apixaban 2.5 mg twice daily, edoxaban 30 mg once daily and [in USA only] dabigatran 75 mg twice daily) with caution, based on pharmacokinetic data. 54. In end-stage renal disease (CrCl <15 ml/min) or dialysis-dependent, we suggest using well-managed VKA with TTR >65–70%. 60. In AF patients who have previously refused OAC, we suggest reinforcing educational messages at each contact with the patient and revisit OAC treatment decisions.	consensus-based statement 49. Ungraded consensus-based statement 52. Ungraded consensus-based statement 54. Ungraded consensus-based statement 60. Ungraded consensus-based statement
Asia Pacific Heart Rhythm Society 2021 [217] Asia-Pacific region	2.1.1 'A' Avoid stroke with anticoagulation, that is, well-managed warfarin (TTR >65%–70%) or DOAC 6.1.1. In patients with AF with mechanical heart valves or moderate-to-severe mitral stenosis, warfarin is recommended. 6.1.2. For stroke prevention in patients with AF without significant VHD (i.e., mechanical heart valves or moderate-to-severe mitral stenosis; so-called "valvular AF") who are eligible for OAC, DOACs are recommended in preference to vitamin K antagonists (VKAs). 6.1.6. In patients with AF with a CHA_2DS_2-VASc score of 1 in men or 2 in women, OAC should be considered for stroke prevention. Different age thresholds for different comorbidities may help guide DOACs use (e.g. age 35 years for heart failure, 50 years for hypertension or diabetes mellitus and 55 for vascular diseases). 6.1.7. If a VKA is used, a target INR of 2.0–3.0 is recommended, with individual TTR ≥65% (ideally ≥70%). A high SAMe-TT_2R_2 score (>2) is associated with a likelihood of poor TTR, and such patients have more attention to ensure good quality anticoagulation (e.g. education and counselling, more frequent INR checks) or to reconsider the decision to prescribe DOACs (if suitable). 6.1.8. In patients on VKAs with low time in INR therapeutic range (e.g. TTR <70%), recommended options are as follows: a. Switching to an DOAC but ensuring good adherence and persistence with therapy; b. Efforts to improve TTR (e.g. education/counselling and more frequent INR checks). 7.1.1. The use of VKA is recommended in patients with moderate to severe mitral stenosis and mechanical heart valve. 7.1.2. For optimal management of VKA therapy, INR of 2.0–3.0 is recommended in Asian patients with AF, with attention to ensure TTR is ≥65%. 10.1.1. Because DOACs are more effective and safer than warfarin in Asian patients with AF, DOACs are the recommended choice of OAC in Asian patients with AF. 10.1.2. The Cockroft–Gault equation should be adopted to calculate CCr to determine the dosing of DOACs. 10.1.3. On-label or guideline-adherent dosing of DOACs is recommended in Asian patients. For patients with acute coronary syndrome or for percutaneous coronary intervention: 11.1.1 In patients with AF eligible for DOACs, it is recommended to use a DOACs in preference to a VKA in combination with antiplatelet therapy. 11.1.2. In patients with high bleeding risk (HAS-BLED ≥3), rivaroxaban 15 mg o.d. should be considered in preference to	NR

	rivaroxaban 20 mg o.d. for the duration of concomitant single or DAPT, to mitigate bleeding risk. 11.1.3. In patients with high bleeding risk (HAS-BLED ≥3), dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant single or DAPT, to mitigate bleeding risk. 11.1.4. In patients with AF with an indication for a VKA in combination with antiplatelet therapy, the VKA dosing should be carefully regulated with a target INR of 2.0–2.5 and TTR > 70%. For patients undergoing atrial fibrillation ablation: 12.1.1. We recommend a preferential use of DOACs over VKA because of their safety profile relative to VKA in addition to their ease of management before and after ablation. 12.1.2. DOAC dosing protocols, uninterrupted or minimally interrupted, should be determined in each institution, depending on the volume of AF ablation done, experience of the operator, backup system in case of life-threatening complications, baseline renal function and thromboembolism and bleeding risks of each patient, time of administration of once-daily DOACs (morning or evening), preparation of specific antidotes to DOACs, etc. a. For most patients, an uninterrupted DOAC strategy may be the preferred option. 12.1.3 When VKA is used, it should be controlled within a therapeutic range and uninterrupted throughout the periprocedural period unless bleeding events preclude its continuous use. 17.1.1. For outpatients with AF during the COVID-19 pandemic, DOAC therapy in replacement of VKA (unless contraindicated) may be considered.	
Canadian Cardiovascular Society/Canadian Heart Rhythm Society 2020 [215] Canada	13. We recommend that individualised goals of care and specific approaches to management should be developed in collaboration with patients and should consider their values and preferences to enhance engagement and improve adherence to long-term therapy. 15. We recommend that adherence and persistence to pharmacotherapy be assessed at each clinical encounter and supported using patient-centred strategies. 18. We recommend that OAC be prescribed for most patients with AF and age 65 years or older or $CHADS_2$ score ≥1. 21. We recommend most patients should receive a DOAC (apixaban, dabigatran, edoxaban or rivaroxaban) in preference to warfarin when OAC therapy is indicated for patients with NVAF. 22. We recommend that warfarin be used for patients with a mechanical prosthetic valve and those with AF and moderate to severe mitral stenosis. 27. We recommend a DOAC in preference to a VKA when an OAC is indicated for AF patients with coronary or arterial vascular disease. 36. When an OAC is indicated in the presence of active malignancy, we suggest a DOAC in preference to a VKA. 39. When OAC is indicated for atrial arrhythmias in adults with simple or moderate forms of CHD, we suggest a DOAC in preference to a VKA in the absence of recent cardiac surgery (<3 months), a mechanical valve, and atrioventricular (AV) valve stenosis with enlarged and diseased atria.	13. Strong Recommendation; Low-Quality Evidence 15. Strong Recommendation; Low-Quality Evidence 18. Strong Recommendation; Moderate-Quality Evidence 21. Strong Recommendation; High-Quality Evidence 22. Strong Recommendation; Moderate-Quality Evidence 27. Strong Recommendation; High-Quality Evidence 36. Weak Recommendation; Low-Quality Evidence 39. Weak Recommendation; Moderate-Quality Evidence 47. Weak

	47. When a decision has been reached that a patient will be undergoing unplanned pharmacological or electrical cardioversion of AF, we suggest that therapeutic anticoagulation therapy be initiated immediately (preferably before cardioversion) with either: (1) a DOAC; or (2) heparin followed by adjusted-dose VKA. Recommendations for interruptions for VKA or DOAC for an invasive procedure are not reproduced here.	Recommendation; Low-Quality Evidence
European Society of Cardiology/European Association for Cardio-Thoracic Surgery 2020 [4] Europe	*Recommendations for the prevention of thrombo-embolic events in AF* 1. For stroke prevention in AF patients who are eligible for OAC, DOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis). 2. OAC should be considered for stroke prevention in AF patients with a CHA_2DS_2-VASc score of 1 in men or 2 in women. Treatment should be individualised based on net clinical benefit and consideration of patient values and preferences. 3. If a VKA is used, a target INR of 2.0–3.0 is recommended, with individual TTR ≥70%. In patients on VKAs with low time in INR therapeutic range (e.g. TTR <70%), recommended options are: 4. Switching to a DOAC but ensuring good adherence and persistence with therapy; or 5. Efforts to improve TTR (e.g. education/counselling and more frequent INR checks). *Recommendations for stroke risk management peri-cardioversion* 6. In patients with AF undergoing cardioversion, DOACs are recommended with at least similar efficacy and safety as warfarin. *Recommendations for patients with AF and an acute coronary syndrome, percutaneous coronary intervention, or chronic coronary syndrome* 7. In AF patients eligible for DOACs, it is recommended to use a DOAC in preference to a VKA in combination with antiplatelet therapy *Note that recommendations specific to dosage of DOACs and VKA has not been included here* *Recommendations for secondary stroke prevention in AF patients after acute ischaemic stroke* 8. In AF patients with an ischaemic stroke or TIA, long-term secondary prevention of stroke using OAC is recommended if there is no strict contraindication to OAC use, with a preference for DOACs over VKAs in DOAC-eligible patients 9. In AF patients presenting with acute ischaemic stroke, very early anticoagulation (<48 h) using UFH, LMWH or VKAs is not recommended *Recommendations for stroke prevention in AF patients after intracranial haemorrhage* 10. In AF patients at high risk of ischaemic stroke, (re-) initiation of OAC, with preference for DOACs over VKAs in DOAC-eligible patients, should be considered in consultation with a neurologist/stroke specialist after: A trauma-related ICH Acute spontaneous ICH (which includes subdural, subarachnoid, or intracerebral haemorrhage), after careful consideration of risks and benefits *Recommendations for patients with valvular heart disease and AF* 11. DOACs are contraindicated in patients with a prosthetic mechanical valve	1. Class I Grade A 2. Class IIa Grade B 3. Class I Grade B 4.Class I Grade B 5. Class IIa Grade B 6. Class I Grade A 7. Class I Grade A 8. Class I Grade A 9. Class III Grade B 10. Class IIa Grade C 11. Class III Grade B

	12. Use of DOACs is not recommended in patients with AF and moderate-to-severe mitral stenosis. *Recommendations for the management of AF during pregnancy* 13. Therapeutic anticoagulation with heparin or VKA according to the stage of pregnancy is recommended for patients with AF	12. Class III Grade C 13. Class I Grade C
National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand 2018 [216] Australia and New Zealand	*Stroke prevention – anticoagulation* 1. Oral anticoagulation therapy to prevent stroke and systemic embolism is recommended in patients with non-valvular AF (N-VAF) whose CHA2DS2-VA score is 2 or more, unless there are contraindications to anticoagulation. 2. When oral anticoagulation is initiated in a patient with N-VAF, a DOAC—apixaban, dabigatran or rivaroxaban—is recommended in preference to warfarin 3. Warfarin is recommended and DOACs should not be used in patients with valvular AF (mechanical heart valves or moderate to severe mitral stenosis). 4. Point-of-care INR measurement is recommended in the primary care management of patients receiving warfarin *Anticoagulation in special situations—CKD* 5. Warfarin should be used if an AF patient with severe CKD requires anticoagulant therapy. *Note that recommendations pertaining to bridging in anticoagulated patients requiring surgical procedures is not described here*. 6. Treatment goals should be developed in partnership with patients and communicated with all members of the multidisciplinary team.	1. High, strong 2. Quality moderate, strength strong 3. Moderate, Strong 4. Moderate, strong 5. Low, strong 6. Low, strong
National Institute for Health and Care Excellence/Royal College of Physicians 2021 [219] UK	1.2.3 Offer monitoring and support to modify risk factors for bleeding, including poor control of INR in patients on vitamin K antagonists 1.2.4 Discuss the results of the assessments of stroke and bleeding risk with the person taking into account their specific characteristics, for example comorbidities, and their individual preferences. 1.4.3 To support adherence and ensure safe and effective medicines use in people with atrial fibrillation, follow the recommendations in NICE's guidelines on medicines adherence and medicines optimisation 1.6.3 Offer anticoagulation with a DOAC to people with atrial fibrillation and a CHA_2DS_2-VASc score of 2 or above, taking into account the risk of bleeding. Apixaban, dabigatran, edoxaban and rivaroxaban are all recommended as options, when used in line with the criteria specified in the relevant NICE technology appraisal guidance *Note that a link to a separate document provides recommendations for use of DOACs in patients with renal impairment* 1.6.4 Consider anticoagulation with a DOAC for men with AF and a CHA_2DS_2-VASc score of 1, taking into account the risk of bleeding. Apixaban, dabigatran, edoxaban and rivaroxaban are all recommended as options, when used in line with the criteria specified in the relevant NICE technology appraisal guidance 1.6.5 If DOACs are contraindicated, not tolerated or not suitable in people with atrial fibrillation, offer a VKA 1.6.6 For adults with AF who are already taking a VKA and are stable, continue with their current medication and discuss the option of switching treatment at their next routine appointment, taking into account the person's time in therapeutic range 1.6.9 Assessing anticoagulation control with VKAs. Calculate the person's TTR at each visit. 1.6.10 Reassess anticoagulation for a person whose anticoagulation is poorly controlled	NR

	1.6.11 When reassessing anticoagulation, take into account an,d if possible, address the following factors that may contribute to poor anticoagulation control 1.6.12 If poor anticoagulation control cannot be improved, evaluate the risks and benefits of alternative stroke prevention strategies and discuss these with the person	

Abbreviations:

AF: atrial fibrillation; **CHA_2DS_2-VASc**: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/transient ischaemic attack, Vascular disease, Age 65–74 years, Sex category (female); **CKD**: chronic kidney disease; **CrCl**: creatinine clearance; **DOAC**: direct oral anticoagulants; **HAS-BLED:** Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly (>65 years), Drugs/alcohol concomitantly**; INR**: international normalised ratio; **NICE**: National Institute for Health and Care Excellence; **NVAF**: non-valvular atrial fibrillation; **OAC**: oral anticoagulant; **TTR**: time in therapeutic range; **VHD**: valvular heart disease; **VKA**: vitamin K antagonist

Notes:

[a] **Quality of evidence**:

Grade A: Data sourced from randomised clinical trial/s or meta-analyses.

Grade B: Data sourced from well-designed controlled study without randomisation, quasi-experimental study or non-experimental descriptive study.

Grade C: Consensus of opinion/reports of experts or clinical experience of authorities.

[b] **Strength of recommendation**:

Strong (1): Benefits outweigh harms;

Conditional (2): Benefits balanced with harms

Class I: Evidence that a given treatment is beneficial

Class IIa: Conflicting evidence; weight of evidence is in favour of efficacy

Class III: Evidence is that treatment is not effective and in some cases may be harmful

20 Appendix G: Ongoing and recently completed clinical trials and studies

Table 136 Ongoing clinical trials and studies meeting the inclusion criteria

Trial registry ID; Country	Indications; Sample size (n) Trial design	Intervention	Comparator	Primary outcome(s)		Recruitment status; Expected completion date
NCT04593043 United States	Atrial fibrillation n=78,140 NRSI	Dabigatran	Warfarin	Stroke and systemic embolism		Active, not recruiting Estimated completion date 1 Feb 2021
NCT04593030 United States	Atrial fibrillation n=22,518 NRSI	Apixaban	Warfarin	Stroke and systemic embolism		Active, not recruiting Estimated completion date 1 Sept 2021
NCT04593056 United States	Atrial fibrillation n=102,636 NRSI	Rivaroxaban	Warfarin	Stroke and systemic embolism		Active, not recruiting Estimated completion date 1 Sept 2021
NCT03563937 Germany	NVAF n=64,920 NRSI	Apixaban Rivaroxaban Edoxaban	Phenprocoumon	Stroke or systemic embolism Fatal bleeding		Not recruiting. Actual completion 10 Dec 2019
NCT02754154 Not reported	NVAF n=321,182 NRSI	Apixaban Dabigatran Rivaroxaban	Warfarin	Time to first bleeding event		Not recruiting Actual completion 26 Dec 2018
NCT04878497 United States	Atrial fibrillation in older frail patients n=1,000,000 NRSI	Apixaban Dabigatran Rivaroxaban	Warfarin	Stroke or systemic embolism Major/life-threatening bleeding All-cause mortality		Not recruiting Estimated completion date Dec 2022
NTR6721 The Netherlands	Frail elderly patients with atrial fibrillation n=2,750 NRSI	DOAC	VKA	Major/life-threatening bleeding Clinically-relevant non-major/life-threatening bleeding		Recruiting Study completion date unpublished
ACTRN12616-000452493 Australia	Older people with AF initiating an oral anticoagulant n=1,000 NRSI	Apixaban Dabigatran Rivaroxaban	Warfarin	Major/life-threatening bleeding Clinically-relevant non-major/life-threatening bleeding		Not yet recruiting Study completion unpublished

Trial registry ID; Country	Indications; Sample size (n) Trial design	Intervention	Comparator	Primary outcome(s)		Recruitment status; Expected completion date
JPRN-UMIN00-0021649 Japan	Heart failure with atrial fibrillation n=70 RCT	Rivaroxaban	Warfarin	Various plasma marker levels Cardiovascular death Hospitalisation due to cardiovascular disease		Recruiting Study completion unpublished
EUCTR2015-005566-33-DE Germany	Patients with acute coronary syndrome and atrial fibrillation n=400 RCT	Apixaban	Phenprocoumon	Bleeding events Composite clinical efficacy outcome		Not recruiting Actual completion date 13 Dec 2021
NCT03847181 UK	NVAF n=45,164 NRSI	Rivaroxaban Apixaban	Warfarin	Intracranial haemorrhage Ischaemic events		Completed Actual completion date 31 October 2020

Abbreviations:
DOAC: direct-acting oral anticoagulant; **NRSI**: non-randomised studies of interventions; **NVAF**: non-valvular atrial fibrillation; **RCT**: randomised controlled trial; **VKA**: vitamin K antagonist.