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Health Technology Assessment (HTA)

HTA Protocol

Title	Oral anticoagulants for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation
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Executive Summary

In Switzerland both vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) are publicly reimbursed for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF). Due to the high costs associated with DOACs, and observational data from Germany reporting superior effects of VKAs over DOACs across multiple outcomes for patients with NVAF, the Federal Office of Public Health (FOPH) has contracted an independent evaluation of DOAC use in the Swiss population. This protocol outlines the proposed method for a health technology assessment (HTA) report evaluating the safety, effectiveness, costs, cost-effectiveness and budget impact of DOACs compared to VKAs in patients with NVAF.

For the evaluation of clinical effects, a systematic literature search of four databases (Pubmed, Embase, Cochrane Library, INAHTA Database) will be conducted with no date limitations. Although two VKAs are approved for use in Switzerland (i.e. acenocoumarol and phenprocoumon), scoping searches indicate there is limited randomised controlled trial (RCT) evidence comparing these drugs to DOACs. As such, warfarin will be considered to be a substantially equivalent substitute, which will be included in the HTA where evidence for acenocoumarol and phenprocoumon is not available. Where possible systematic reviews will form the basis of the clinical evaluation in the HTA report. Where existing reviews do not exist, de novo meta-analyses of primary evidence (i.e. randomised and/or non-randomised studies) comparing DOACs to VKAs will be conducted.

For the economic evaluation, systematic literature searches of four databases (Pubmed, Embase, INAHTA Database, Econlit) will identify existing economic studies that are directly applicable to the policy question; where none exist, an independent evaluation will be required. The approach will be finalised during the HTA phase, and is likely to comprise a cost-utility analysis. The analysis will utilise up-to-date Swiss-specific cost inputs and will utilise clinical inputs that are most applicable to the Swiss context. Finally, a budget impact analysis will be conducted.

For the evaluation of legal, social, ethical and organisational domains, relevant issues will be identified from the studies included in the clinical evaluation. In addition, targeted non-systematic searches will be conducted to identify grey literature related to these domains; key issues will be summarised narratively.

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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
IHE	Institute of Health Economics
INR	International normalised ratio
IS	Ischaemic stroke
MCMC	Markov chain Monte Carlo
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
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
TSOAC	Target-specific oral anticoagulant
UK	United Kingdom
VKA	Vitamin K antagonist
WHO	World Health Organisation

Objective of the HTA Protocol

Based on a preliminary screening of the literature the objective of the HTA protocol is to formulate the research question, to define the population, intervention, comparator, outcomes (PICO) and describe the methodology to conduct a systematic literature search, extract, analyse and synthesise the data in the health technology assessment (HTA) report on the topic. Key questions are defined, addressing the main HTA domains, i.e. efficacy/effectiveness/safety, costs/budget impact/cost-effectiveness, ethical/legal/social and organisational issues.

1 Policy question

Each health technology assessment (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 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 DOACs were associated with significantly higher likelihood of adverse events for patients with NVAF.[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 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. AF has three typical patterns of presentation: paroxysmal (spontaneously resolves within seven 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, hypertension and endocrine disorders. 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), 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 lungs, resulting in a stroke or systemic embolism, respectively.[5] Patients with AF may be asymptomatic, or they may experience symptoms such as chest pain, palpitations, a fast heart rate, shortness of breath, nausea, dizziness, severe sweating and fatigue.[5,9]

AF is associated with an increased risk of stroke (five-fold) and heart failure and death (two-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 suffer from AF, corresponding with 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 two- to three-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 aged 60–70 years and in 10-17% of those aged 80 years or older.[4,6] It is estimated that nearly 20% of individuals over the age of 65 years will have AF by 2030, with 120,000 to 215,000 new cases expected annually.[16]

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).[17]

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%).[18,19] 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%).[18,19]

Between 10% and 40% of patients with AF are hospitalised annually due to heart failure, arrhythmia recurrence, stroke and bleeding events.[20] A German registry trial conducted between 2009 and 2012 reported 18.5% of patients followed for one year after enrolment were hospitalised, noting that 12% of hospital admissions were related to treatments for AF.[21] Hospitalisations account for 50-70% of the total costs of caring for patients with AF.[22] 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.[23] 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.[24,25] Overall, the estimated annual cost of AF to healthcare systems in Europe range from EUR660 to 3,286 million, absorbing up to 2.6% of total annual healthcare expenditures.[25]

4 Technology description

Clot formation to control bleeding from a damaged blood vessel involves multiple interlinked steps within the following three broadly defined stages: initiation (disturbance of the vascular endothelium and clotting factors); activation of various proenzymes to produce thrombin; and fibrin clot formation.[26-29] There are two main pathways in the clotting cascade: the intrinsic pathway and the extrinsic pathway. External trauma activates the extrinsic pathway and involves factor VII.[29] 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).[27,29] 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.[26-29]

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.[4,8,30] Since oral anticoagulation increases 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[31] is used to assess embolic risk in patients with AF, with oral anticoagulation being recommended (i.e. Class IA) when patients have NVAF and a CHA_2DS_2-VASc score ≥2 (men) or ≥3 (women), and considered (i.e. Class IIa) for a score of 1 (men) or 2 (female) (maximum score of 9).[4] The HAS-BLED[B] score[32] 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,[33] noting that adequate medical counselling, patient self-management and adherence to treatment plans are necessary for stable disease management.[34,35]

[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).

[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.

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.[13,36] 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.[13,26,33]

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 (see ***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 oral anticoagulants that inhibit clotting factors IIa (thrombin) or Xa. DOAC is the term preferred by the International Society of Thrombosis and Haemostasis.[26,37] 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 thrombin inhibitors 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.[26] **Direct factor Xa Inhibitors,** which include rivaroxaban, apixaban, edoxaban, and betrixaban, bind directly to factor Xa to inhibit the cleavage of prothrombin to thrombin.[26,29]

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 with NVAF.[4,8,30] Four DOACs are approved in Switzerland: rivaroxaban (Xarelto®), edoxaban (Lixiana®), apixaban (Eliquis®) and dabigatran (Pradaxa®) (see ***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.[38]

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% Metabolism, biliary/intestinal 35%	Yes	
Acenocoumarol (Sintrom®) [b] Medius AG	1-8 mg once daily	8-11 hours	Renal 65% Metabolism, 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	30-60 mg once daily	10-14 hours	Renal 50% Metabolism, 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					
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] Note that Warfarin is not approved for use in Switzerland. [b] Note that in Switzerland these drugs are approved for other indications in addition to NVAF.
Sources: Black et al. 2019[28], Hindricks et al. 2021[4], Raschi et al. 2019[38], Ray & Keyrouz 2014[39], Steffel et al. 2021[30], Swissedic 2021[40], Ufer 2005[41]

4.2 Anticoagulant utilisation in Switzerland

In Switzerland, VKAs and DOACs are prescribed for the prevention of stroke and systemic embolism 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.[16,42] 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.

5 PICO criteria

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 oral anticoagulation
Intervention(s)	Dabigatran (Pradaxa®) – 110-150 mg twice daily Apixaban (Eliquis®) – 2.5-5 mg twice daily Edoxaban (Lixiana®) – 30-60 mg once daily Rivaroxaban (Xarelto®) – 15-20 mg once daily
Comparator(s)	Acenocoumarol (Sintrom®) – 1-8 mg once daily Phenprocoumon (Marcoumar®) – 1.5-4.5 mg once daily Warfarin – 1.5-12 mg once daily †
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 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. Serious adverse events Health economic outcomes 1. Direct medical 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: † Studies on warfarin will only be considered for inclusion where there is no evidence for phenprocoumon or acenocoumarol.

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).[40] The term valvular 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 four DOACs approved in Switzerland for NVAF will be included: dabigatran 110-150mg twice daily, apixaban 2.5-5 mg twice daily, edoxaban 30-60 mg once daily, rivaroxaban 15-20 mg once daily. While the three direct factor Xa Inhibitors (apixaban, edoxaban and rivaroxaban) share a similar mechanism of action, each drug will be 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.

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. 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 will be grouped as a class comparator for the RCT evidence, including warfarin. For the non-randomised studies of interventions (NRSI), only acenocoumarol and phenprocoumon will be included, as there is evidence available for these drugs. This strategy avoids the large evidence gap that would be present among studies of higher levels of evidence if only acenocoumarol and phenprocoumon are used as comparators. Trials using suboptimal doses of VKAs (target INR <2 or >3[4]) will be excluded.

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).[20,45,46] The list of outcomes provided in the PICO criteria (***Table 2***) follow European Medicines Agency and

European Society of Cardiology guidance on relevant outcome measures for patients with AF.[20,45,46] 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 will be 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 oral anticoagulation?
2. Are DOACs safe compared to VKAs for the prevention of stroke and other thromboembolic events in patients with NVAF who are eligible for oral anticoagulation?
3. Are there any adherence or persistence 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 Methodology

7.1 Clinical evaluation

The proposed methods have been developed with reference to the Cochrane Handbook for Systematic Reviews of Interventions,[47] and are described 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 will be conducted in four databases (PubMed, Embase, Cochrane Library, INAHTA database) with no date restrictions. The search strategy includes 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 are planned to be used during the searches. Searches will also be 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. ***Appendix A*** outlines the search strategy for PubMed, which will be adopted to Embase and the Cochrane Library accordingly during the HTA phase, as well as the INAHTA database, and trial registries.

7.1.2 Study selection

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

Where eligible systematic reviews are not available, primary studies that meet the PICO criteria will be included. Additionally, the searches will seek 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.

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	Patients with moderate/severe mitral stenosis or a mechanical prosthetic heart valve
Intervention(s)	Dabigatran (Pradaxa®) – 110-150 mg twice daily Apixaban (Eliquis®) – 2.5-5 mg twice daily Edoxaban (Lixiana®) – 30-60 mg once daily Rivaroxaban (Xarelto®) – 15-20 mg once daily	Non-oral preparations; betrixaban
Comparator(s)	Acenocoumarol (Sintrom®) – 1-8 mg once daily Phenprocoumon (Marcoumar®) – 1.5-4.5 mg once daily Warfarin – 1.5-12 mg once daily †	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 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. Serious 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	Inadequate data, incomplete reporting, or unclear follow-up duration, other outcomes
Design/Publication type	Clinical evidence Systematic reviews with a NMA or meta-analysis † of RCTs and NRSIs. Where suitable reviews are not available, RCTs and NRSIs will be 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, letter to the editor, expert opinion, editorial, narrative review articles

Language	English, French, German and Italian language studies[49]	All other languages
Country	WHO Mortality Stratum A‡	Non-Stratum A countries
Year	All	None

Abbreviations: AF: atrial fibrillation; 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 Organisation.

Notes: † Up-to-date is defined as a systematic review that captured enough contemporary evidence such that any studies published after the search dates are unlikely to significantly change the magnitude or direction of the results of the review. Quality will be evaluated against the AMSTAR-II appraisal criteria.[50] Articles with no critical insufficiencies (e.g. in relation to selection criteria, search strategy, etc) will be eligible for inclusion. ‡ 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 will be excluded during full-text screening because the cause of death and burden of disease in these countries are not comparable to those in Switzerland.[51]

Results from the literature searches will be imported into Rayyan (Rayyan Systems Inc, United States).[52] Rayyan functions similarly to EndNote but allows for easy blinding of reviewers, and management of study inclusion conflicts. The search results will be screened against the predetermined eligibility criteria (***Table 3***) by two reviewers. To ensure that the inclusion criteria are interpreted consistently between reviewers, two separate training samples (k = 250 and k = 250 citations) will be used to establish inter-rater reliability. Both reviewers will select studies independently in both training samples, with selections compared between reviewers. The first sample will be a training sample only, and the second sample will be used to calculate inter-rater reliability; a minimum Kappa score of 0.7, representing substantial agreement between reviewers,[53] will be required. Further training samples of 250 citations will be used until the minimum Kappa score is achieved, after which point screening of the remainder of articles by title and abstract will be split between the reviewers. In cases where a reviewer is unsure about whether to include an article, the article will be included for further review by full-text. Following the title and abstract screen, all articles deemed potentially relevant will then be reviewed by full-text by each reviewer independently. Conflicts between reviewers on study inclusion will be settled via consensus. If consensus cannot be reached, a third reviewer will decide whether to include or exclude the citation. The reasons for excluding articles at full-text review will be documented, and the results of the study selection will be reported in a PRISMA flow diagram.

7.1.3 Data extraction

One reviewer will independently extract data (on a study-arm level, where applicable) into a standardised template, which will be checked against the original study record by a second reviewer. Disagreements will be settled by discussion or utilisation of a third independent reviewer. Data of interest include:[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 atrial fibrillation), prior myocardial infarction, prior stroke or transient ischaemic attack.
- 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 report outcomes graphically instead of numerically, *WebPlotDigitizer* will be used to estimate numerical values.[55]

7.1.4 Assessment of quality of evidence

The assessment of the quality of evidence will be performed by one reviewer and checked by a second reviewer. Any differences will be settled via consensus. If consensus cannot be reached, a third reviewer will be consulted. The quality and risk of bias of included evidence will be assessed using different tools depending on the research design. Systematic reviews will be evaluated against the AMSTAR-II appraisal criteria, RCTs will be evaluated using Cochrane Risk of Bias 2.0 (RoB 2.0),[56] and NRSI will be evaluated using the Cochrane Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) tool.[57] Quality assessments of primary studies conducted by included systematic reviews will not be repeated unless they were conducted with a tool that is not listed above.

The overall certainty of the reported outcomes will be appraised using the GRADE approach. If existing NMAs are included, a modified GRADE approach for network meta-analysis described by Salanti et al. 2014 will be used. This modified GRADE approach acknowledges: (i) what each piece of direct evidence contributes to the analysis; (ii) the central role indirect comparisons plays in the analysis; (iii) the prospect of disagreement between indirect and direct evidence; and (iv) how the validity of the network meta-analysis is affected by the assumption of transitivity.[47,58] The modified GRADE assessment will include consideration of the following domains, with each domain being rated as ‘high’, ‘low’ or ‘unclear’:

1. Within-study and across-study risk of bias
2. Joint consideration of indirectness and intransitivity
3. Joint consideration of statistical heterogeneity and statistical inconsistency
4. Imprecision
5. Publication bias.

The results of the assessments for each domain will be compiled into an overall evaluation of the certainty of the evidence (i.e. an overall GRADE score), ranging between 'high', 'moderate', 'low' and 'very low'. Two GRADE 'summary of findings' tables will be produced, one based on the available RCT evidence, and one based on the available observational evidence. Each table will include the following outcomes:

1. Cardiovascular-related mortality
2. Major/life threatening bleeding
3. Systemic embolic events
4. Ischaemic stroke
5. Haemorrhagic stroke
6. Adherence
7. Serious adverse events

7.1.5 Data analyses of efficacy, effectiveness and safety outcomes

7.1.5.1 Data synthesis

The method of data synthesis will depend on whether relevant systematic reviews with NMAs or meta-analyses are available. *De novo* analysis will not be performed if existing systematic meet the inclusion criteria. In such cases, the results from included systematic reviews will be reported for the relevant outcomes outlined in ***Table 3***, and synthesised into a GRADE summary of findings table.

A *de novo* meta-analysis will be performed for specific outcomes of interest of primary research reports of RCTs and NRSIs, where there are no existing systematic reviews with meta-analyses available.

Meta-analysis will be performed using R software. Random-effects models using the generic inverse variance method will be used as the basis for the primary analysis. Fixed-effects models using the generic inverse variance method will only be used in cases where it is reasonable to assume that the studies are measuring the same treatment effect, i.e. due to low clinical and statistical heterogeneity between included studies; in all other cases, random-effects models will be used. Meta-analysis will be performed for outcomes reported by at least two studies.

Except for health-related quality of life (HRQoL), all outcomes included in the review will be dichotomous. Each dichotomous outcome will be reported as a risk ratio with 95% confidence intervals, and the unit of measurement will be the number of patients experiencing an event. Health-related quality of life will be reported as mean difference between treatment arms with 95% confidence intervals. Where included studies report different HRQoL scales, standardised mean differences with 95% confidence intervals will be used. Standardised mean differences will be interpreted using generic standard deviation units, and also re-expressed as the most commonly reported scale of HRQoL included in the analysis. All

outcomes will be reported at longest follow-up; analyses may be stratified by duration, depending on data availability.

7.1.5.2 Assessment of heterogeneity

Heterogeneity will be 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 as proposed in the Cochrane handbook (I^2 = 0–40% might not be important; 30–60% moderate; 50–90% substantial; 75–100% considerable heterogeneity). Where substantial heterogeneity is evident, the causes of this will be explored through subgroup analysis, described in ***Section 7.1.5.4***.

7.1.5.3 Publication bias

Publication bias in will be assessed using tests for funnel plot asymmetry, for outcomes with a minimum of 10 studies. In addition, clinical trial registries will be searched to identify unpublished studies/outcomes as a means of narratively describing publication bias.

7.1.5.4 Subgroup and sensitivity analysis

Subgroup analysis will be conducted to investigate potential causes of heterogeneity based on the following potential effect modifiers from meta-analyses of RCTs:

- Age; per decade above 50[59]
- Sex[59]
- Body mass index[59]
- Hypertension[59]
- Previous stroke or transient ischaemic attack[59]
- Previous myocardial infarction[59]
- Chronic heart failure[59]
- Impaired renal function[59]
- $CHADS_2$ score[59]
- CHA_2DS_2-VASc score[59]
- HAS-BLED score[59]

Sensitivity analyses will be conducted to investigate the impact of methodological factors on the reported results of the clinical evaluation of RCTs.[46] These will include:

- Risk of bias due to confounding
- Risk of bias due to selection bias

- Risk of bias due to information bias
- Follow-up duration

7.1.5.5 Imputation methods for dealing with missing values

Missing SDs will be obtained from available means, sample sizes, standard errors and 95% confidence intervals (95% CIs) using formulae detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.1).* In situations where data are not available to calculate SD, it will be imputed using the 'impute_SD' function in the *R* (version 1.4) package 'metagear', following the imputation methods described by Braken et al. 1992.[60-63] Where continuous values need to be combined, formulae detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.1)* will be used. For studies that report outcomes graphically, *WebPlotDigitizer* will be used to convert graph points into numerical values.[55]

7.1.5.6 Narrative synthesis

If fewer than two studies report an outcome, meta-analysis will not be possible. In such cases, the results will be tabulated and described narratively in text. For continuous outcomes, the mean change from baseline or final follow-up score and standard deviation will be reported for each study arm, as well as the mean difference and 95% confidence interval comparing the mean effects between groups. For dichotomous outcomes event rates for each trial arm will be reported, along with a risk ratio and 95% confidence interval comparing the event rates between groups.

7.2 Economic evaluation

The systematic literature searches outlined in ***Section 7.1.1*** and ***Appendix A*** will be used to identify studies relevant to the cost-effectiveness of DOACs compared to VKAs in patients with NVAF eligible for anticoagulation. Searches will be conducted in four databases (PubMed, Embase, INAHTA database, Econlit). The review of economic evidence will carry two sequential intents: (1) to identify any existing Swiss economic evaluations addressing the research question, and (2) in the absence of such studies, to identify contemporary models to guide an independent economic evaluation.

When reviewing the economic literature, only recent (published in the last 10 years) full economic evaluations (cost-effectiveness, cost-utility, or cost-benefit analyses) meeting the PICO criteria and performed within the context of a World Health Organisation (WHO) Mortality Stratum A country will be considered. Studies meeting these criteria will be grouped based on certain characteristics (e.g., included drugs, perspective, modelling technique), allowing similarities and differences across studies

to be assessed. This review process will be undertaken to inform the modelling approach for the HTA, rather than to provide a critical summary of the existing literature. Therefore, formal appraisal of existing economic studies will not be conducted.

In the absence of any evaluations that are directly applicable to the Swiss context, an independent evaluation would be the most appropriate path forward due to the limitations of applying evaluation results from other models to the Swiss context. Various assumptions and costs specific to the Swiss context and health system would be best incorporated into the assessment of cost-effectiveness through an independent economic evaluation.

Below, we outline key methodological considerations for an independent economic evaluation, were this to be required.

7.2.1 Methodological considerations for an independent economic evaluation

Population

The independent evaluation will consider Swiss patients with NVAF who are eligible for anticoagulation. The exact characteristics of the model cohort will be confirmed during the HTA. In a previous Swiss study, patient characteristics were derived from sub-samples of a clinical trial (the RE-LY trial).[64] Recent studies evaluating cost-effectiveness amongst multiple DOACs from the perspectives of neighbouring countries to Switzerland (Austria and Italy),[65,66] as well as the UK,[44,67,68] have derived patient properties from a published network meta-analysis.[44,67]. Inherently, these approaches assume that patients in the included RCTs are representative of the NVAF population within the country of interest. During the HTA, key demographic characteristics of the model cohort will be compared with circumstances of use in Switzerland. Information on the demographic profile of Swiss patients with NVAF will be sought during the HTA.

An assessment of the cost-effectiveness of DOACs compared to VKAs in certain population subgroups may be of relevance to the policy question. If so, these population subgroups will align with those considered in the clinical evaluation.

Intervention

The intervention in this HTA will be all relevant DOACs. In line with previous models,[65-67,69-71] it is proposed that each DOAC should be considered individually.

Comparator

The comparator will be VKA therapy. VKA therapy will be treated as a drug class, so an average cost across phenprocoumon and acenocoumarol will be used, based on Swiss utilisation data. The cost of VKA therapy will include the costs associated with INR monitoring.

Whilst phenprocoumon and acenocoumarol are the only approved VKAs in Switzerland, warfarin is the most prescribed VKA worldwide; most clinical evidence for VKAs is specific to warfarin. Clinical input parameters informed by the clinical evaluation will likely be based upon a DOAC versus warfarin comparison. The applicability of the clinical evidence to the Swiss context will be assessed during the HTA by comparing clinical characteristics of the included trials to Swiss practice. Potential uncertainties or concerns regarding the applicability of this evidence to Switzerland will be reflected in sensitivity analyses. NRSIs specific to phenprocoumon and acenocoumarol (***Section 5.3***) may be considered for scenario analysis. Furthermore, the quality of INR control in daily Swiss practice compared to INR control within the clinical evidence could be explored.

Outcome of the economic evaluation

The proposed approach will be a cost-utility (CUA) analysis. In line with previous evaluations, [65-67,69-71] a Markov model will most likely be used for the analysis; however, this will be confirmed during the HTA. We will assess the incremental costs, incremental effects (measured using the QALY), and ICERs (expressed as the cost per QALY gained) of each DOAC versus VKA therapy for Swiss patients with NVAF eligible for anticoagulation.

The analysis will be conducted from a Swiss healthcare payer perspective. Direct medical costs for services covered by the OKP will be included, irrespective of the actual payer (which may include health insurers, cantons, or patients). Non-medical and indirect costs will not be considered. Costs will be reported in Swiss Francs (CHF) for a common costing year.

The model will incorporate results from the clinical evaluation on the efficacy and safety of DOACs compared to VKA therapy to predict the costs incurred and QALYs lived by Swiss patients treated for NVAF over a lifetime horizon. Costs and utilities will be assigned to the heath states and events included in the economic model to facilitate the analysis. These health states and events will capture the main clinical outcomes in anticoagulated patients with NVAF, such as stroke and severe bleeding events. Cost data will be sourced from Swiss diagnosis related group (DRG) costs for inpatient services, the Spezialitätenliste for medicine costs, the Analysenliste for laboratory costs, and TARMED for outpatient services. Utility values will most likely be derived from previous economic models.

In discussion with the FOPH, it was agreed that the purpose of an economic evaluation would be to compare each DOAC with VKA therapy.. Accordingly, the HTA report will present four ICERs reflecting the comparisons between each DOAC and VKA therapy. Both one-way deterministic sensitivity analyses and probabilistic sensitivity analyses will be employed to explore uncertainty within each individual DOAC versus VKA comparison.

Summary

In summary, the proposed methodology for an independent economic evaluation will be to construct an economic model aligning closely in structure to published models. An overview of the proposed modelling methodology is provided in ***Table 4***.

Table 4 Summary of the proposed economic evaluation methodology

Perspective	Swiss healthcare payer
Patient population	Swiss patients with NVAF who are eligible for anticoagulation
Intervention	• Apixaban • Dabigatran • Edoxaban • Rivaroxaban
Comparator	VKA therapy †
Type of economic evaluation	CUA
Time horizon	Lifetime
Sources of inputs	Published meta-analyses, RCTs, observational studies, Spezialitätenliste, Analysenliste, TARMED, Swiss DRGs, expert opinion
Costs	Direct medical costs (CHF) (Pharmaceutical costs; laboratory costs; outpatient and inpatient medical care costs)
Effect measure	QALYs
Discount rate	3.0% p.a. for both costs and QALYs

Abbreviations: CHF: Swiss francs; CUA: cost-utility analysis; DRG: diagnosis-related group; NVAF: non-valvular atrial fibrillation; RCT: randomised controlled trial; VKA: vitamin K antagonists; QALYs: quality-adjusted life years.
Notes: † Clinical data used in the economic model will include warfarin as a relevant comparator. It has been determined that, for the purpose of this HTA, warfarin is substantially equivalent to phenprocoumon and acenocoumarol.

7.2.2 Budgetary impact analysis

Both the intervention (DOACs) and comparators (VKAs; phenprocoumon and acenocoumarol) are reimbursed for use in patients with NVAF via the Spezialitätenliste. Usage data for Switzerland for the intervention and comparator drugs will be sourced from © COGE GmbH. Tarifpool. © SASIS AG. Methods to estimate the proportion of total usage attributable to patients with NVAF will be explored during the HTA. Projected costs (CHF) to the payer of oral anticoagulation in patients with NVAF over the next five years under current policy/practice conditions will be evaluated. Payer costs for oral anticoagulation overall, and for DOACs and VKAs separately, will be reported.

The appropriateness of evaluating the potential financial implications of any policy/practice changes will be informed by findings of the clinical and economic evaluations.

7.3 Legal, social, ethical and organisational issues

The systematic literature searches outlined in ***Section 7.1.1*** and ***Appendix A*** will be used to identify studies relevant to the legal, social, ethical, and organisational issues related to NOAC and VKA use in patients with NVAF. In addition, targeted, non-systematic keyword searches for grey literature addressing these domains will be conducted (sources are listed in ***Appendix A***, ***Table 9***). Relevant studies will be tabulated, which describe the study characteristics and key findings, and the results will be synthesised narratively.

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9 Appendices

9.1 Appendix A: Literature Search Strategy

Table 5 Search strategy (PubMed)

Population	1.	Atrial fibrillation[tw]
	2.	Auricular fibrillation[tiab]
	3.	Atrium fibrillation[tiab]
	4.	non-valvular[tiab]
	5.	nonvalvular[tiab]
	6.	NVAF[tiab]
	7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6
Intervention	8.	New oral anticoagulant*[tiab]
	9.	Novel oral anticoagulant*[tiab]
	10.	Non-vitamin K oral anticoagulant*[tiab]
	11.	Non-vitamin K antagonist*[tiab]
	12.	Direct oral anticoagulant*[tiab]
	13.	Oral anticoagulant*[tiab]
	14.	DOAC*[tiab]
	15.	NOAC*[tiab]
	16.	OAC*[tiab]
	17.	Rivaroxaban[tiab]
	18.	Xarelto[tiab]
	19.	Apixaban[tiab]
	20.	Eliquis[tiab]
	21.	Edoxaban[tiab]
	22.	Lixiana[tiab]
	23.	Dabigatran[tiab]
	24.	Pradax*[tiab]
	25.	Prazax*[tiab]
	26.	IIa inhibitor*[tiab]
	27.	thrombin inhibitor*[tiab]
	28.	Factor Xa inhibitor*[tw]
	29.	10a inhibitor*[tiab]
	30.	direct coagulation[tiab]
	31.	antithrombin*[tw]
	32.	anti-thrombin*[tiab]
	33.	#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
Comparator	34.	Vitamin-K antagonist*[tiab]
	35.	VKA[tiab]
	36.	Phenprocoumon[tw]

	37.	Phenprocumon[tiab]
	38.	Acenocoumarol[tw]
	39.	Acenocumarol[tiab]
	40.	Warfarin[tw]
	41.	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
Language	42.	English[la]
	43.	German[la]
	44.	French[la]
	45.	Italian[la]
	46.	#42 OR #43 OR #44 OR #45
Limits	47.	Animals[mh]
	48.	Humans[mh]
	49.	#47 NOT (#47 AND #48)
	50.	editorial[pt]
	51.	letter[pt]
	52.	news[pt]
	53.	congress[pt]
	54.	#50 OR #51 OR #52 OR #53
Combined search string	55.	#7 AND #33 AND #41 AND #46
	56.	#55 NOT #49
	57.	#56 NOT #54

Table 6 Search strategy (INAHTA database)

Population	1.	Atrial fibrillation
Intervention	2.	New oral anticoagulant*
	3.	Novel oral anticoagulant*
	4.	Non-vitamin K oral anticoagulant*
	5.	Non-vitamin K antagonist*
	6.	Non-vitamin-K antagonist*
	7.	Direct oral anticoagulant*
	8.	Oral anticoagulant*
	9.	DOAC*
	10.	NOAC*
	11.	OAC*
	12.	Rivaroxaban
	13.	Xarelto
	14.	Apixaban
	15.	Eliquis
	16.	Edoxaban
	17.	Lixiana
	18.	Dabigatran
	19.	Pradax*
	20.	Prazax*

	21.	IIa inhibitor*
	22.	thrombin inhibitor*
	23.	Xa inhibitor*
	24.	10a inhibitor*
	25.	direct coagulation
	26.	antithrombin*
	27.	anti-thrombin*
	28.	#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
Comparator	29.	Phenprocoumon
	30.	Acenocoumarol
	31.	#29 OR #30
Combined search string	32.	#1 AND #28 AND #31

Table 7 Search strategy ClinicalTrials.gov and EU Clinical Trials Register

Population	1.	Atrial fibrillation
Comparator †	2.	Phenprocoumon
	3.	Acenocoumarol
	4.	Warfarin
Combined search string	5.	#1 AND (#2 OR #3 OR #4)

Notes: † Clinical trial databases do not allow for searches to be run with complex Boolean logic. Intervention terms are not included in the clinical trials search as the policy question is primarily interested in direct comparisons between the DOACs and either phenprocoumon, acenocoumarol or warfarin; therefore, searching for only the comparator drugs is a highly sensitive and specific strategy for searching these registers for relevant studies.

Table 8 Search strategy EconLit (EBSCO)

Population	1.	Atrial fibrillation
Intervention	2.	New oral anticoagulant*
	3.	Novel oral anticoagulant*
	4.	Non-vitamin K oral anticoagulant*
	5.	Non-vitamin K antagonist*
	6.	Direct oral anticoagulant*
	7.	Oral anticoagulant*
	8.	DOAC*
	9.	NOAC*
	10.	OAC*
	11.	Rivaroxaban
	12.	Xarelto
	13.	Apixaban
	14.	Eliquis
	15.	Edoxaban

	16.	Lixiana
	17.	Dabigatran
	18.	Pradax*
	19.	Prazax*
	20.	IIa inhibitor*
	21.	thrombin inhibitor*
	22.	Xa inhibitor*
	23.	10a inhibitor*
	24.	direct coagulation
	25.	antithrombin*
	26.	anti-thrombin*
	27.	#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
Combined search string	28.	#1 AND #28

Table 9 Grey literature sources

Source	Website
Google	https://www.google.com/
Trip Database	https://www.tripdatabase.com/
European Society of Cardiology	https://www.escardio.org/
American College of Cardiology	https://www.acc.org/
NHS Pathways	https://www.nhspathways.org/
Afib Matters	https://www.afibmatters.org/
European Association for Cardio-Thoracic Surgery	https://www.eacts.org/
Australian Heart Foundation	http://www.heartfoundation.org.au/
NPS Medicinewise	https://www.nps.org.au/
European Medicines Agency	https://www.ema.europa.eu/
Federal Statistical Office	https://www.bfs.admin.ch/bfs/en/home.html
HTA websites of INAHTA members	
Australia	
Adelaide Health Technology Assessment (AHTA)	https://www.adelaide.edu.au/ahta/pubs/
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S)	https://www.surgeons.org/research-audit/research-evaluation-inc-asernips
Austria	
Austrian Institute for Health Technology Assessment (AIHTA)	https://aihta.at/page/homepage/en
Gesundheit Österreich GmbH (GOG)	http://www.goeg.at
Argentina	
Institute for Clinical Effectiveness and Health Policy (IECS)	http://www.iecs.org.ar

Belgium	
Belgian Health Care Knowledge Centre (KCE)	http://kce.fgov.be
Brazil	
National Committee for Technology Incorporation (CONITEC)	http://conitec.gov.br/en/
Agência Nacional de Saúde Suplementar/ National Regulatory Agency for Private Health Insurance and Plans (ANS)	https://www.gov.br/ans/pt-br
Canada	
Institute of Health Economics (IHE)	http://www.ihe.ca
Institut National d'Excellence en Santé et en Services (INESSS)	https://www.inesss.qc.ca/en/home.html
The Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/
Ontario Health (OH)	https://www.ontariohealth.ca/
Colombia	
Instituto de Evaluación Tecnológica en Salud (IETS)	http://www.iets.org.co
Denmark	
Social & Health Services and Labour Market (DEFACTUM)	http://www.defactum.net
Finland	
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/HTA-julkaisuja.aspx
France	
French National Authority for Health (Haute Autorité de Santé; HAS)	http://www.has-sante.fr/
Assistance Publique – Hôpitaux de Paris	http://cedit.aphp.fr
Germany	
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA)	https://www.g-ba.de/english/
Ireland	
Health Information and Quality Authority (HIQA)	http://www.hiqa.ie
Italy	
Agenzia Sanitaria e Sociale Regionale (ASSR)	http://www.inahta.org/members/assr/
HTA Unit in A. Gemelli Teaching Hospital (UVT)	https://www.policlinicogemelli.it/
National Agency for Regional Health services (Agenas)	http://www.agenas.it
Kazakhstan	
Ministry of Public Health of the Republic of Kazakhstan, Republican Centre for Health Development (RCHD)	http://www.rcrz.kz

Korea	
National Evidence-based healthcare Collaborating Agency (NECA)	www.neca.re.kr/eng
Malaysia	
Health Technology Assessment Section, Ministry of Health Malaysia (MaHTAS)	http://www.moh.gov.my
The Netherlands	
The Netherlands Organisation for Health Research and Development (ZonMw)	http://www.zonmw.nl
Zorginstituut Nederland (ZIN)	https://www.zorginstituutnederland.nl/
Norway	
The Norwegian Institute of Public Health (NIPHNO)	http://www.fhi.no/
Peru	
Institute of Health Technology Assessment and Research (IETSI)	http://www.essalud.gob.pe/ietsi/
Poland	
Agency for Health Technology Assessment and Tariff System (AOTMiT)	http://www.aotm.gov.pl
Republic of China, Taiwan	
Center for Drug Evaluation (CDE)	http://www.cde.org.tw
Russian Federation	
Center for Healthcare Quality Assessment and Control (CHQAC)	www.rosmedex.ru
Singapore	
Agency for Care Effectiveness (ACE)	Agency for Care Effectiveness (ACE) (ace-hta.gov.sg)
Spain	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud “Carlos III”I / Health Technology Assessment Agency (AETS)	http://publicaciones.isciii.es/
Agency for Health Quality and Assessment of Catalonia (AQuAS)	http://aquas.gencat.cat
Andalusian HTA Agency	http://www.aetsa.org/
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.eus/web01-a2ikeost/en/
Galician Agency for Health Technology Assessment (AVALIA-T)	http://acis.sergas.es
Health Sciences Institute in Aragon (IACS)	http://www.iacs.es/
Sweden	
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
Switzerland	

Swiss Federal Office of Public Health (SFOPH)	http://www.bag.admin.ch/hta
Tunisia	
INEAS – National Authority for Assessment and Accreditation in Healthcare, TUNISIA	http://www.ineas.tn/fr
United Kingdom	
Healthcare Improvement Scotland (HIS)	http://www.healthcareimprovementscotland.org
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
Health Technology Wales (HTW)	http://www.healthtechnology.wales
National Institute for Health Research (NIHR), including HTA programme	http://www.nets.nihr.ac.uk/programmes/hta
United States	
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/research/findings/index.html
Uruguay	
Health Assessment Division, Ministry of Public Health (HAD)	http://www.msp.gub.uy

Abbreviations: HTA: health technology assessment; INAHTA: International Network of Agencies for Health Technology Assessment.