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The effective, safe and appropriate use of anticoagulation medicines.

A systematic overview of reviews

Ginny Brunton, Michelle Richardson, Gillian Stokes, Laurence Blanchard, Helen Burchett, Meena Khatwa, Claire Khouja, Ruth Walker, Kath Wright, Amanda Swoden, James Thomas.

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The authors of this report are:
Ginny Brunton[1], Michelle Richardson[1], Gillian Stokes[1], Laurence Blanchard[2], Helen Burchett[2], Meena Khatwa[1], Claire Khouja[3], Ruth Walker[3], Kath Wright[3], Amanda Sowden[3], James Thomas[1]

[1] - EPPI-Centre, UCL Institute of Education
[2] – London School of Hygiene and Tropical Medicine
[3] – Centre for Reviews and Dissemination, University of York

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Glossary

An *anticoagulant* is an agent that prevents the clotting of blood.[1]

Antiplatelet agents (e.g., aspirin or clopidogrel) reduce platelet aggregation and, therefore, the formation of clots.[1]

Atrial fibrillation is a heart condition that causes an irregular and often abnormally fast heart rate.[2]

Clinically relevant bleeding often refers to acute or subacute, clinically observable bleeding that does not meet the criteria for major bleeding, and that requires hospital admission, doctor-led medical or surgical treatment, or changes in antithrombotic treatment.[3]

Deep vein thrombosis is a blood clot that develops within a deep vein in the body, usually in the leg.[4]

Direct evidence refers to the results obtained from direct comparisons in a study, i.e. the two interventions are assessed one versus the other (e.g., apixaban v warfarin).

An *embolism* is the condition in which an embolus becomes lodged in an artery and obstructs its blood flow. The most common form of embolism is *pulmonary embolism*, in which a blood clot is carried in the circulation to lodge in the pulmonary artery. An embolus in any other artery constitutes a *systemic embolism*.[1]

Genotype is the genetic constitution of an individual or group, as determined by the particular set of genes it possesses.[1]

Genotyping is the process of determining differences in the genetic make-up (*genotype*) of an individual by examining the individual's DNA sequence, using biological assays, and comparing it to another individual's sequence or a reference sequence.

Indirect evidence refers to the results obtained from an estimation of the comparison of two interventions, using a comparator that both have in common in other studies (e.g., apixaban v edoxaban in the definition for *network meta-analysis*).

International normalised ratio is a measure of how long it takes for blood to begin to form clots. Prothrombin is a plasma protein produced by the liver. Clotting is caused by a series of clotting factors which activate each other, including the conversion of prothrombin to thrombin. The test used to measure the activity of this clotting factor is called the prothrombin time (PT). The international normalised ratio (INR) is a highly-controlled version of the PT, using standardised ingredients, and the results are exactly reproducible no matter which laboratory or in which country the test is performed. The INR is specifically used to measure the exact effect of warfarin in the blood. The higher the INR the less likely that there will be a clot, but the more likely a bleed. Many patients have a target INR of 2.0 – 3.0 as an ideal compromise for reducing the chances of a clot while

[1] Oxford Concise Medical Dictionary (2015)

[2] https://www.nhs.uk/conditions/atrial-fibrillation/

[3] http://heart.bmj.com/content/103/8/623

[4] https://www.nhs.uk/conditions/deep-vein-thrombosis-dvt/

being safe with respect to bleeding. The target range may be lower or higher than this depending on individual circumstances.[5]

Low-molecular-weight heparin is a type of heparin that is more readily absorbed and requires less frequent administration than standard heparin preparations used as *anticoagulant* therapy.[1]

Major bleeding can be defined as clinically observable bleeding at a critical site (e.g., intracranial) or that leads to death, with a reduction in haemoglobin level by at least 2g/dL or requiring a transfusion of at least two units of packed red blood cells.[3]

Meta-analysis is a method used to synthesise direct pair-wise comparisons for a given outcome (e.g., apixaban v warfarin, or edoxaban v warfarin).

Network meta-analysis can estimate indirect comparisons between interventions that have a common comparator (e.g., apixaban v edoxaban in the *meta-analysis* example, using warfarin as the common comparator), allowing the coverage of a wider range of interventions.

Novel oral anticoagulants, also called non-vitamin K antagonist *oral anticoagulants*, include apixaban, dabigatran, edoxaban, and rivaroxaban.

Oral anticoagulation therapy is an *anticoagulant* that is taken by mouth. Warfarin is the main oral anticoagulant used in the UK.[6] It is a *vitamin K antagonist*, other vitamin K antagonists include phenprocoumon and acenocoumarol, and non-vitamin K antagonists include apixaban, dabigatran, edoxaban, and rivaroxaban.

Pharmacist-managed anticoagulation services include drug dose adjustment based on INR measurements interpreted by the pharmacist, medication/drug interaction review and providing patient and/or healthcare provider education through clinic visits or telephone follow-up.

Primary prevention is avoidance of the onset of disease by behaviour modification or treatment.[1]

A *pulmonary embolism* is a blocked blood vessel in the lungs. It can be life-threatening if not treated quickly.[7]

Quality-adjusted life-year is a year of life adjusted by the quality of life that a patient experiences with their medical condition.

Randomised controlled trials are studies in which a number of similar people are randomly assigned to two (or more) groups to test a specific drug, treatment or other intervention.

Rankograms are two-dimensional treatment-specific plots, presenting on the horizontal axis the possible ranks of the treatment, and on the vertical axis, the probability for the treatment to assume each of the possible ranks according to a specific outcome.[8]

[5] https://labtestsonline.org.uk/tests/pt
[6] https://www.nhs.uk/conditions/warfarin/
[7] https://www.nhs.uk/conditions/pulmonary-embolism/
[8] http://methods.cochrane.org/cmi/glossary

Routine medical care in the USA is provided in anti-thrombosis clinics by physicians and nurses. In the UK, it can be provided by GPs or in specialist clinics or hospitals, according to UK guidelines.[9]

Secondary prevention is the avoidance or alleviation of disease by early detection and appropriate management.[1]

Self-management involves testing by the patient at home, with the patient making any dose adjustments according to rules based on their INR measurement.[10]

Self-monitoring is the equivalent of self-testing.

Self-testing is testing by the patient at home and communicating the results to a physician who returns any dose adjustments.

A *systemic embolism* is a blockage in any artery other than the pulmonary artery, see *embolism.*

Time in therapeutic range can be determined by the Rosendaal et al. (1993) method, which is also known as linear interpolation, this is a way of calculating the percentage of time that a patient's INR is within the set therapeutic range (usually 2.0 to 3.0), based on the measurements taken and the time between these measurements.[11]

Venous thromboembolism is a condition in which a blood clot forms in a vein. This is most common in a leg vein, where it's known as deep vein thrombosis. A blood clot in the lungs is called pulmonary embolism.[12]

Vitamin K antagonists are *anticoagulants* that include warfarin, phenprocoumon and acenocoumarol.

[9] https://www.westsuffolkccg.nhs.uk/wp-content/uploads/2013/01/Anticoagulants-guideline-on-the-mgmt-of-pts-tx-with-warfarin-phenindione-acenocoumarol.pdf
[10] Heneghan et al. 2016
[11] https://www.inrpro.com/rosendaal.asp
[12] https://www.nhs.uk/Tools/Pages/VTE-self-assessment.aspx

Abbreviations

AF	Atrial fibrillation
AMS	Anticoagulant medical service
ApoE	Apolipoprotein E
bd	Bis die or bis in diem or twice daily
CBT	Cognitive behavioural therapy
CRB	Clinically relevant bleeding
DAOCs	Direct-acting oral anticoagulants
DVT	Deep vein thrombosis
HTA	Health Technology Assessment
INR	International normalised ratio
LMWH	Low-molecular-weight heparin
MD	Mean difference
MI	Myocardial infarction
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NOACs	Novel oral anticoagulants
NR	Not reported
OAC	Oral anticoagulant
OAT	Oral anticoagulation therapy
od	Omne in diem or once daily
PMAS	Pharmacist-managed anticoagulation services
PMWT	Pharmacist-managed warfarin therapy
PE	Pulmonary embolism
QALY	Quality-adjusted life-year
RCTs	Randomised controlled trials
n-RCTs	Non-randomised controlled trails
RMC	Routine medical care
SE	Standard error
TTR	Time in therapeutic range
UCM	Usual care medicine
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WMD	Weighted mean difference

Abstract

Background
Current NICE guidelines recommend the use of both warfarin and novel oral anticoagulants (NOACs) for the prevention and treatment of stroke related to atrial fibrillation (AF), and for venous thromboembolism (VTE). This review was commissioned to assess uncertainties about the evidence on the efficacy, safety and patient/clinician experience in adults with AF or VTE.

Methods
We undertook a rapid overview of systematic reviews, searching four databases for systematic reviews published from 2014 and using a comprehensive review on oral anticoagulants (OACs) efficacy and safety by Sterne et al. (2017). Data extraction frameworks were developed for each dimension examined. The quality of reviews was assessed using criteria for quantitative, mixed-methods or qualitative evidence syntheses, as appropriate. Results were synthesised narratively and thematically.

Results
Twenty-three reviews were included in this overview. In relation to efficacy and safety, the findings of Sterne's review indicate that NOACs show advantages over warfarin for the prevention of AF-related stroke for most efficacy and safety outcomes, especially apixaban (5mg bd). There is no strong evidence to support the use of NOACs for VTE for primary prevention, acute treatment and secondary prevention. Ten genotyping reviews were assessed, however, none provided evidence specific to AF and VTE populations. There was limited, low-quality evidence, from six reviews of self-management, indicating that education, or education plus patient decision aids, were beneficial for AF populations. Results were mixed among mixed-diagnoses groups. Pharmacist-managed anticoagulation may be beneficial, compared with usual care, among mixed-diagnoses groups. No review evaluated pharmacist-managed anticoagulation services exclusively among populations with AF and no interventions exclusively targeted a VTE population. Evidence from nine reviews of stakeholder experiences suggests that patients and most clinicians value drug efficacy first, followed by safety. There were no clear patterns regarding which factors are most important for patients' decisions around OACs or OAC adherence.

Conclusion
This overview of reviews informs policy decisions in the choice of OACs for the prevention and treatment of AF-related stroke and VTE. It also identifies dimensions for clinicians to consider when prescribing and monitoring OACs in terms of their and patients' needs and preferences.

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Executive Summary

Background

NICE guidelines recommend the use of oral anticoagulants for the treatment of an irregular heartbeat (atrial fibrillation, hereafter AF), and for clots arising in large veins (venous thromboembolism, hereafter VTE). Warfarin, a vitamin K antagonist, was until recently the only available oral drug for anticoagulation. Novel oral anticoagulants (NOACs) have been introduced, in recent years, as alternatives to warfarin. Four NOACs are currently licensed for use in England: dabigatran, rivaroxaban, apixaban and edoxaban.

In the UK, AF is the most common cardiac arrhythmia and is associated with approximately 12,500 strokes every year. The underutilisation of anticoagulants, in patients with AF at high risk of stroke, has been identified as a major gap in clinical care. VTE was responsible for 44,000 hospital admissions, in 2013, and its recurrence is an important cause of long-term morbidity.

Current NICE guidelines recommend the use of both warfarin and NOACs for the prevention and treatment of AF and VTE. However, since the last update in 2014, several uncertainties relating to their efficacy, safety and patient experience have been raised. Firstly, warfarin requires frequent blood monitoring to maintain levels of anticoagulation within a narrow range of therapeutic effect, in order to reduce the risk of stroke and risk of bleeding. NOACs do not require close monitoring, although concerns have been raised that the lack of monitoring may reduce adherence. Secondly, warfarin's action can be altered by a number of medications, food and alcoholic drinks, which requires adjustments by the patient and clinician. NOACs do not require such adaptations but their potential adverse interactions are also less known than those of warfarin, due to their recent availability.

NOACS are currently more expensive than warfarin, as they are newer. However, due to changing patient preferences, the regular monitoring required for warfarin, the interactions of warfarin with medications, food and drinks, and a potentially greater risk of severe haemorrhage with warfarin, there is a growing shift towards prescribing NOACs.

Data from several potentially influential trials on patients who took anticoagulants for AF and VTE have been reviewed since the last update of NICE guidelines in 2014. This current literature review was commissioned to assess the clinical evidence, published since then, on the efficacy, safety, and patient/clinician experience of warfarin and NOACs in order to guide optimal decision making among NHS commissioners, clinicians and patients.

Methods

We undertook a rapid overview of reviews. We searched four electronic databases for citations published from 2014 onwards. Combinations of free-text and database-specific

terms were developed around the concepts of: (oral anticoagulants and synonyms) AND (condition where appropriate) AND (systematic review). Potentially relevant documents were also received from Department of Health and Social Care collaborators.

Titles and abstracts were screened and were coded according to their main focus (e.g., drug efficacy, drug safety, patient adherence, genotyping, patient/clinician experience). Since the efficacy and safety of oral anticoagulants were recently assessed in a comprehensive systematic review commissioned via the NIHR Health Technology Assessment Programme (Sterne et al. 2017), we summarised and critiqued this review for evidence on efficacy and safety. Full reports were retrieved for the remaining included citations and these were screened. Citations were excluded if they:

- were published prior to 2014
- were not available in English
- focused specifically on non-OECD settings
- did not focus on adults eligible for oral anticoagulation
- did not focus on oral anticoagulants for the prevention of stroke related to AF or the acute treatment and primary and secondary prevention of VTE
- did not focus on one of the following five anticoagulants: warfarin, dabigatran, rivaroxaban, edoxaban, or apixaban
- were not a systematic review
- did not assess therapeutic doses of warfarin compared with NOACs
- did not include health or cost outcomes

Data extraction frameworks were developed to code included reviews according to specified characteristics. Included reviews were assessed for methodological quality using AMSTAR or AMSTAR2 criteria, or quality assessment criteria for mixed-methods reviews and qualitative evidence syntheses, as appropriate.

The synthesis focused on efficacy, safety, self-monitoring, genotyping, and patient and clinician experience reviews. Reviews were brought together in two stages. First, we descriptively mapped the characteristics of all reviews, in order to understand the different aims, populations, settings, interventions and comparisons, and patient outcomes or experiences. This process identified over 400 recent systematic reviews of efficacy and safety. In consultation with NHS commissioners, the decision was made to focus on the most recent, rigorous and comprehensive overview of systematic reviews located, which addressed our research questions (Sterne et al. 2017). Next, we mapped the characteristics from all review types to the policy priorities highlighted in our research questions, to understand where evidence exists that addresses these priorities and where there are gaps.

To assure review quality, searches were developed by an information scientist using free text and thesaurus terms; manual screening on title and abstract and then full reports, and

quality assessment, were undertaken by two reviewers until agreement was reached, then single screening was undertaken; syntheses were conducted by at least two researchers; and EPPI-Reviewer© specialist software (Thomas et al. 2010) was used to manage data. External academics, clinician advisors, and NHS and Department of Health and Social Care stakeholders were consulted throughout the review process. The overview protocol was registered on PROSPERO. No changes were made to the protocol during the conduct of the overview, although findings for efficacy and safety were based on a single recent comprehensive high quality systematic review (Sterne et al. 2017) rather than an overview of multiple reviews.

Results

Efficacy and Safety

The findings of Sterne's review indicate that NOACs show advantages over warfarin for the prevention of AF-related stroke and systemic embolism for most efficacy and safety outcomes. Of these, apixaban (5mg bd) offers the best balance between efficacy and safety and had the highest probability of being most cost-effective. There was no strong evidence to support the use of NOACs for VTE for primary prevention (compared with low-molecular-weight heparin; assessed for hip- and knee-surgery patients only), acute treatment (compared with warfarin) and secondary prevention (compared with warfarin and aspirin). However, in terms of safety, apixaban (5mg bd) and rivaroxaban (15mg bd, then 20mg od) may reduce the risk of major and clinically relevant bleeding, compared with warfarin, for the acute treatment and secondary prevention of VTE. For secondary prevention of VTE, aspirin was likely to be the most cost-effective alternative to warfarin.

Despite the high quality of Sterne's review, the breadth of important issues studied, and the inclusion of many high-quality trials, several effect estimates were imprecise. This was mainly due to the unavailability of direct comparisons between the NOACS, the reliance on short-term trial data, and the limited generalisability of trial data to clinical contexts. Sterne et al. (2017) concluded that prescribers and patients may, therefore, choose to exercise caution when considering the results of these reviews.

Genotyping

Genotyping has the potential to provide information about risks and treatment, in specific populations, carrying specific genes. However, the review evidence that currently exists on genotyping-guided dosing is not specific to patient populations with AF and VTE. Available reviews address important questions related to genotyping, including whether clinical outcomes vary between patients who are treated with standard dosing vs. genotype-guided dosing, and whether warfarin dose requirement varies between patients with different gene variants. The issue of inter-ethnic variation in dose requirement was also addressed. In order to appropriately investigate these important questions and make meaningful recommendations for AF and VTE patients, rigorous evaluations of pharmacogenetics, focused in these patient populations, are needed.

Self- or pharmacist-managed interventions

In analyses focused specifically on AF populations, there appears to be limited evidence, of low quality, to support the beneficial effects of education and education plus patient decision aids on time in therapeutic range (TTR). Results from one study, of uncertain quality, indicated that there was little evidence to support the effectiveness of self-testing on improving time in INR, compared with usual care, but it did not perform worse. In terms of self-management, the results from three low-quality primary studies suggested it was uncertain whether or not self-management may improve TTR, compared with usual care.

Among mixed-diagnoses groups, the low-to-moderate quality evidence suggested that self-testing interventions may improve the INR values in therapeutic range, compared with usual care. However, findings from moderate-quality evidence were more mixed, with both positive (longer) and negative (shorter) time in therapeutic range for the self-testing intervention, compared with usual care. The evidence for self-management interventions was mixed for types of outcomes, with both higher and lower INR numbers in therapeutic range, and shorter and longer time in therapeutic range, compared with usual care. Low-quality meta-analytic evidence indicated that self-management may be as effective as usual care but does not offer enhancements over and above usual care, in terms of TTR. The variation in findings suggests the presence of potential moderators operating.

The review-level evidence for pharmacist-managed anticoagulation, as an alternative to usual physician care,[13] was more consistent. Findings from mixed-quality studies, rated as high and uncertain, suggest that pharmacist-managed anticoagulation may improve TTR, compared with usual care, among mixed-diagnoses groups. There were no reviews evaluating pharmacist-managed anticoagulation services exclusively for populations with AF and none of the interventions were exclusively examined in populations with VTE.

Stakeholder perspectives

Reviews of patient and physician perceptions, preferences and values, and reviews of interventions assessing these outcomes, found that when initiating or switching OAC medication, patients and most clinicians value drug efficacy above other factors. This was followed by safety (i.e. risk of bleeding). Many other factors were important to patients/clinicians when initiating, continuing or switching OAC therapy. These included their knowledge, experience, changes in patient cognition and memory due to the condition itself, patient characteristics such as age, gender, lifestyle, employment status, support needs, or patient-clinician factors such as communication and perceptions about who bears the responsibility for decision-making. No clear patterns emerged about which were most important in patients' decisions about initiating, switching or continuing OAC therapy, and to facilitate patient adherence with treatment.

[13] Although pharmacist management may not strictly be self-management, it can be easier to access for patients and could reduce pressure on GP or specialist services, and is, therefore, included here in self-monitoring.

Due to the variability in factors that might influence a decision to either initiate warfarin therapy, switch to NOAC therapy, or continue with any OAC therapy, some review authors suggested that where efficacy and safety are equal, there is a need for individualised discussions with patients, which should include a tailored framing of all potential risks associated with treatment. Most review authors recommended that these factors be integrated into decision-making tools, to help structure discussions with patients about therapy and allow both patients and physicians to clarify their preferences and values. However, evaluations of interventions addressing preferences and values have shown limited success. This may be influenced by communication styles, a clarification of which factors matter most to each patient, and the extent to which patients and clinicians feel that the decision to adopt or switch OAC therapy is their responsibility.

Discussion

The findings of this overview of reviews support the use of NOACs for the prevention of stroke in AF patients, especially apixaban (5mg bd). There is no evidence supporting the use of NOACs for primary prevention, acute treatment and secondary prevention of VTE. The impact of warfarin versus NOACs use on INR clinics' capacity, and in patients with impaired renal function, was not addressed by Sterne and colleagues. Regarding self-monitoring pathways, small improvements were seen but no clear recommendations can be drawn for education, self-monitoring, self-testing and pharmacist-led management due to the limited, mixed evidence found. As for stakeholder perspectives, results suggest that efficacy, followed by safety, are the factors that patients and clinicians mainly base their decisions on. Decisions may also depend on the extent to which patients and clinicians feel it is their individual or shared responsibility. No review-level data were identified about experiences of the impact of NOACs and warfarin on patient lifestyle, and few data on patient quality of life or clinician perceptions of NOACs and warfarin. The currently available evidence syntheses on genotypes are not generalisable to AF and VTE populations.

Where efficacy and safety of specific oral anticoagulation therapies have been established, the next priority should be to consider which factors matter to patients and clinicians in their decision to initiate or maintain a therapy. This could help clinicians to determine the level of support and information to provide to patients, including communication of risks, benefits and preferences. The lack of recognition of these factors, and the need to assess these for each patient, drug and medical condition may explain the limited effects of self-monitoring, self-management, educational and decision-making interventions. Furthermore, age, gender, socio-economic status and ethnicity may be influential in efficacy, safety, and self- and pharmacist-managed interventions, but could not be assessed due to a lack of review-level data.

This overview represents the most up-to-date evidence base on OACs. It has been drawn together using rigorous and transparent methods and takes into account the strength of

evidence. However, since it is an overview of reviews, it does not provide fine detail on populations, interventions and outcomes that may have been reported at primary study level. While the reviews on efficacy and safety (conducted by Sterne et al. 2017) were rated as high quality, authors concluded that prescribers and patients may choose to exercise caution when considering the results of these reviews. This was due to a lack of direct comparisons between NOACs, a reliance on short-term data, and limited generalisability to clinical contexts. Reviews on anticoagulant management approaches, genotyping and perspectives ranged from low to moderate quality. This needs to be considered when interpreting the findings. The substantial overlap in primary studies across the reviews on genotyping merits consideration since this may give undue weight to some findings.

Conclusion

This overview of reviews can be used to inform decisions about the choice of OACs for the prevention and treatment of AF and VTE (efficacy and safety). It also identifies dimensions for clinicians to consider when prescribing and monitoring OAC therapy in terms of patients' needs for support and information (and how to provide the latter), their ability to understand, and preferences for decision-making about therapy.

Some questions could not be addressed, or only limited or mixed evidence was identified. New evidence syntheses could usefully address:

- the impact of OACs on renal functions;
- the efficacy of self-monitoring or self-management for a range of conditions in which VTE is a risk factor;
- differences between genotypes in examining clinical outcomes, treatment maintenance and adverse effects specific to AF and VTE populations; and
- the influence of gender and age on the OACs' efficacy, safety and patient experience.

Research gaps were also apparent and new primary research could address:

- the relationships between age, cognition and memory in AF and VTE populations;
- AF and VTE patients' support needs and preferences with respect to the specific drug therapies recommended by Sterne et al. (2017);
- the most effective strategies to help clinicians assess AF and VTE patients' willingness and ability to decide on OACs therapy;
- self-monitoring and self-management in AF and VTE;
- the limited effectiveness seen in interventions using decision aids; and
- the need for a practical tool to guide clinicians in appraising patients' and their own perceptions of their role and responsibility when decisions must be made regarding the initiation and maintenance of OACs therapy.

Focusing future research efforts in these areas may support clinicians in understanding their choices in prescribing, as well as supporting patients in their need for appropriate information and how it might be provided, in order to aid their understanding and inform decisions about OACs therapy.

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1 Background

Current NICE guidelines recommend the use of oral anticoagulants for the treatment of an irregular heartbeat, and for clots arising in large veins (NICE 2012, 2014, 2015, 2016a). Two types of oral anticoagulants are most commonly prescribed: **warfarin** was until recently the only available oral drug for anticoagulation. This drug is a vitamin K antagonist (VKA): it acts to prevent the carboxylation of clotting factors II, VII, IX, and X by inhibiting vitamin K epoxide reductase (Ha and Bhagavsan 2015). More recently non-vitamin K antagonist oral anticoagulants (NOACs) have been introduced, which are newer alternatives to warfarin. Also known as direct oral anticoagulants, NOACs work as active site-directed inhibitors of thrombin or Factor Xa (Ha and Bhagavsan 2015). Four NOACs are currently licensed for use in England: dabigatran, rivaroxaban, apixaban and edoxaban (NICE 2016b).

Anticoagulation medications are used to prevent strokes related to non-valvular atrial fibrillation (AF) and for the acute treatment and secondary prevention of venous thromboembolism (VTE). AF is the most common cardiac arrhythmia and increases the risk of clot formation within the heart, which can lead to stroke. Risk of thromboembolic stroke is increased five-fold among those with AF, with approximately 12,500 AF-related strokes each year (The Association of the British Pharmaceutical Industry 2014). Strokes experienced by people with AF are typically more severe, with less chance of recovery, higher mortality and morbidity and longer hospital stays, compared to those without AF (Atrial Fibrillation Society 2014). The under-utilisation of anticoagulation therapy in patients with AF at high risk of stroke has been identified as a major gap in clinical care (Lee et al. 2011).

Venous thromboembolism (VTE) occurs when blood clots form in deep veins, usually in the legs or pelvis (known as deep vein thrombosis). These may also be displaced to the pulmonary arteries, resulting in pulmonary embolism. It has been noted that over 44,000 hospital admissions, in 2013, were due to pulmonary embolism or deep vein thrombosis (NICE 2016c). Risk factors for VTE include age (with older people being at a higher risk); patients undergoing major surgery (especially hip fracture surgery, and other illness such as cancer), and hospitalised general medical patients having long periods of inactivity in bed (NHS Confederation 2009). Recurrence of VTE within eight years is estimated at approximately 30% and is an important cause of long-term morbidity, being identified as a risk factor for chronic leg ulceration and pulmonary hypertension (Barnes et al. 2015; NHS Confederation 2009).

Current NICE guidelines (last updated in 2014) recommend the use of both warfarin and NOACs for the prevention and treatment of AF and for the treatment of VTE (NICE 2012, 2014). However, since the publication of the NICE guidance, several uncertainties have been raised relating to the efficacy, safety and patient experience of anticoagulation medicines. These are discussed further below.

Warfarin requires frequent monitoring through blood tests to ensure that treated patients' levels of anticoagulation remain within a narrow range of therapeutic effect. Patients are thought to be less compliant with monitoring due to the frequency with which they must visit outpatient clinics (Abdou et al. 2016). Anticoagulation levels are measured as an international normalised ratio (INR), with a normal range limit of 2 to 3. If the INR falls to less than 2 (under dose), the risk of stroke increases; whereas an INR of more than 3 (overdose) increases the risk of intracranial bleeding. The action of newer, alternative NOACs (dabigatran, rivaroxaban, edoxaban, and apixaban) is much more accurate, reducing the need for such close surveillance (Mekaj et al. 2015). Some authors, however, have expressed concern about adherence to anticoagulation medication in the absence of regular monitoring (Suryanarayan and Schulman 2014). Nonetheless, a recent literature review suggested no reported differences between warfarin and NOACs in terms of patient adherence (Abdou et al. 2016). As an alternative to frequent clinic visits, self-monitoring of warfarin may reduce the demand on anticoagulation clinics (and associated costs). However, despite being recommended by NICE (NICE 2017), it has been suggested that uptake has been low, possibly due to the upfront cost pressures and limited evidence of cost savings.

Due to the complexity of warfarin's mode of action and metabolism, its effect can be altered by a number of medications and food and alcoholic drinks. This can present challenges to patients. For example, a consistent intake of vitamin K and modified alcohol intake is important. Patients need to recheck INR levels when starting new medications, particularly antibiotics. While NOACs do not require these adjustments they have not been available for as long as warfarin, thus less is known about their potential adverse interactions, particularly for patients with other co-morbidities (Willett and Morrill 2017). However, some suggest that this concern may be offset by the lower risk of severe haemorrhage reported within clinical trials of NOACs when compared with warfarin (Graham et al. 2014, Larsen et al. 2014). For example, some studies have shown that for older patients, over the age of 65 years, the risks of ischaemic stroke and intracranial bleeding and mortality were significantly reduced with dabigatran, compared with warfarin (Graham et al. 2014). Furthermore, there is some evidence to suggest that gastrointestinal bleeding is associated with NOACs among AF populations, although this effect has not been observed consistently (Ruff et al. 2014).

NOACS are currently more expensive than warfarin (as they are newer). However, due to changing patient preferences, the regular monitoring required for warfarin, the interactions of warfarin with medications and drinks, and a potential greater risk of severe haemorrhage with warfarin, there is a growing shift towards prescribing NOACs.

Data from several potentially influential trials have been reviewed since the last update of relevant NICE guidelines, in 2014. These may provide important new information to help guide optimal decision making for anticoagulants among NHS commissioners, clinicians and patients. Preliminary scoping searches led to the identification of over 800 systematic

reviews, published from 2014 onwards, that addressed the use of anticoagulants in either AF or VTE (Arnold et al. 2017, Hicks et al. 2016, Verdecchia et al. 2015, Zhang et al. 2015).

Most comprehensively, a recent HTA systematic review concluded that there was no strong evidence that NOACs should replace warfarin for the prevention and treatment of VTE (Sterne et al. 2017). However, among AF populations there is some evidence to suggest that NOACs show advantages over warfarin. Furthermore, recent reviews on patient adherence and the patient/clinician experience of anticoagulants for AF and VTE have been brought together in qualitative evidence syntheses (Borg et al. 2012; Brown et al. 2012; Mas Dalmau et al. 2017), which may add important information about experiences of anticoagulation.

2 Aims of review

Preliminary searches suggest that the research evidence on oral anticoagulants has been synthesised considerably, but it is not clear how these address current policy priorities. To address this need, an overview of reviews was conducted with the aim to assess the clinical evidence, published since the 2014 NICE guidance. Its objective was to highlight where the evidence is cumulative, robust and addresses policy priorities, and note where gaps for future research synthesis or primary research necessitate commissioning.

To address the uncertainties related to the clinical evidence on efficacy, safety and patient/clinician experience of oral anticoagulants, the following research questions were addressed:

1. What evidence syntheses have been conducted to address the efficacy of UK-approved oral anticoagulant therapy with respect to:
    a. Warfarin versus NOACs in different patient cohorts?
    b. The impact of warfarin versus NOACs on INR clinic capacity?
    c. The evidence for an optimised pathway on genotyping?
    d. The evidence for an optimised pathway on self-monitoring?
2. What evidence syntheses have been conducted to address the safety of UK-approved oral anticoagulant therapy with respect to:
    a. Renal function and the long-term use of NOACs?
    b. Complications associated with warfarin and NOACs including bleeding and stroke risk?
3. What are patient and clinician experiences of UK-approved oral anticoagulant therapy concerning:
    a. The impact of NOACs and warfarin on patient lifestyle?
    b. Medicines adherence and compliance of NOACs and warfarin?
    c. Clinician perceptions of NOACs and warfarin?

d. Monitoring INRs in patients receiving VKAs and the effect on patient adherence?

3 Methods

We undertook an overview of existing systematic reviews. This approach provides a systematic and transparent method for bringing together existing evidence rapidly, so is particularly suited for addressing policy questions (Gough and Thomas 2016).

Search

To locate the most recent systematic reviews, relevant electronic sources were searched in October 2017. Searches were limited to four electronic health databases: MEDLINE, Embase, ASSIA and CINAHL. To maximise efficiency, one broad search was conducted in each of the databases to identify systematic reviews addressing efficacy, safety or patient experience. We limited the searches to 2014 onwards (the year in which the most recent relevant NICE guidelines were published). Citations (titles and abstracts) were uploaded into EPPI-Reviewer (specialist systematic review software), for the management of publication retrieval, coding and synthesis (Thomas et al. 2010). Collaborators at the Department of Health and Social Care also provided potentially relevant, published and unpublished research and policy documents for screening. See **Appendix 1** for the MEDLINE search strategy, which was translated for use in the other databases.

Screening for study inclusion/exclusion

Following a pilot screening stage, all citations were screened on the basis of title and abstract. Relevant studies were retrieved, and full-text reports rescreened using the same process. Systematic review citations were assessed for inclusion/exclusion using the criteria in **Table 1** below:

Table 1: Exclusion criteria.

Exclusion criteria	Details
Exclude date of publication	Published prior to 2014
Exclude on language	Is not available in English
Exclude on setting	Review focuses specifically on non-OECD settings.
Exclude on population	Does not focus on adults (18 years or older) eligible for oral anticoagulation
Exclude on topic a)	Does not focus on oral anticoagulants for stroke prevention in atrial fibrillation (AF) or acute treatment and primary and secondary prevention of venous thromboembolism, VTE); where the focus of >50% of included studies is on AF and/or VTE populations or data for these groups are extractable

Exclude on topic b)	Does not focus on one of the following five anticoagulants: warfarin, dabigatran, rivaroxaban, edoxaban, or apixaban
Exclude on method	Is not a systematic review (i.e. authors do not describe search strategy and search at least two databases, inclusion/exclusion criteria and quality assessment methods not reported); OR the citation is a conference abstract)
Exclude on comparator (efficacy and safety synthesis only)	Does not assess therapeutic doses of warfarin compared with NOACs (dabigatran, rivaroxaban, edoxaban, and apixaban)
Exclude on outcomes	Does not include health, patient experience or cost outcomes
Exclude duplicate	Duplicate record

Title and abstract screening resulted in over 400 recent systematic reviews of efficacy and safety. In consultation with NHS commissioners, the decision was made to focus on the most recent, rigorous and comprehensive overview of systematic reviews located, which addressed our research questions (Sterne et al. 2017).

Data extraction

Bespoke data extraction frameworks were developed to code the included reviews according to key characteristics. These descriptive codes allowed us to describe the type and quantity of evidence available, including:

- Year of publication;
- Date range of included primary studies;
- Setting (community, hospital);
- Main topic focus (e.g., efficacy, safety, experiences, or cost);
- Target population (health condition, or at risk group);
- Participant characteristics (e.g., age, and gender); and
- Intervention characteristics (e.g., type of oral anticoagulant, or self-monitoring).

Reviews were additionally coded according to their relevant characteristics of interest, for example:

- Countries of included studies;
- Number of primary studies included in the review;
- Primary study design(s);
- Type of outcomes measured (e.g., mortality, stroke or thromboembolic complications, bleeding, hospitalisation, health-related quality of life, or patient experiences); and
- Extent of overlap of primary studies across reviews.

Relevant characteristics were added as they emerged from the data.

Risk of bias assessment

All relevant reviews were assessed for methodological quality using AMSTAR or AMSTAR2 criteria (Shea et al. 2007; Shea et al. 2017), or quality assessment criteria for reviews of mixed methods and qualitative evidence syntheses (Aromataris et al. 2015). Criteria were summed and categorised as low, medium or high quality, as appropriate. Two reviewers quality-assessed a common set of reviews and met to agree them in order to establish consistency. Once consistency was achieved, one reviewer quality-assessed each review and these assessments were checked by a second reviewer, with discussion to resolve any differences in ratings. Remaining disagreements in ratings were resolved by a third reviewer, where needed. The risk of bias tools are provided in **Appendices 2** and **3.**

Synthesis of evidence

The overview synthesis comprised a descriptive map of reviews organised by the efficacy, safety and cost-effectiveness of oral anticoagulation medication (Chapter 5) genotyping (Chapter 6), efficacy of self-monitoring interventions for the management of anticoagulation medication (Chapter 7), and adherence and patient and clinician experiences (Chapter 8). Reviews were brought together in two stages. First, we mapped the characteristics of the reviews, in order to understand the different aims, populations, settings, interventions and comparisons, patient/clinician outcomes or experiences, and risk of bias ratings. Next, we mapped these characteristics, and the review findings, to the policy priorities highlighted in our research questions to highlight gaps in the existing evidence base.

For reviews of efficacy, safety and cost-effectiveness of oral anticoagulation medication, data were extracted by one reviewer and checked by another (shared between MR, LB and CK). All discrepancies were resolved through discussion. A description of the findings from four systematic reviews with network meta-analyses (NMAs) of randomised controlled trials (RCTs) were extracted. Effect size estimates were not extracted due to the large number of comparisons within each review. Statements about effectiveness were, therefore, reported (as summarised by Sterne and colleagues) by each outcome (stroke, symptomatic VTE, symptomatic deep-vein thrombosis (DVT), symptomatic pulmonary embolism (PE), major, clinically relevant and intracranial bleeding, myocardial infarction, and death from all causes). For details about network plots, and summary statistics, such as odd ratios (ORs) and 95% credible intervals, please refer to Sterne et al. (2017)'s report. Following on from this, Sterne and colleagues' rankogram analyses are presented.[14] The main conclusions of the cost-effectiveness analyses, where carried out, are also reported (please refer to Sterne et al. 2017 for detailed methods). Summaries emphasise the comparisons involving warfarin and NOACs, with reference to other interventions (LMWH and antiplatelets), where informative.

[14] Rankogram analyses calculate the probability that each treatment is best, second best, and so on.

For the reviews of self-monitoring, data were extracted by one reviewer and checked by another (shared between MR and CK). Time in therapeutic range (TTR) was selected as the primary outcome measure, due to consistency in reporting across the reviews and clinical relevance. Data were extracted by condition (AF/VTE), where possible, otherwise data for mixed conditions were extracted. Meta-analytic data were extracted, where available, otherwise the direction of effects and statistical significance were extracted. Findings were synthesised by the type of self-monitoring intervention including education, education and decisions aids, self-testing, self-management, and pharmacist-managed anticoagulation. The findings were synthesised in tables and narratively.

For the reviews of stakeholder perspectives and experiences, two researchers (GB and MK) discussed and devised the coding tool appropriate to the included reviews. After agreeing on the tool, the two researchers independently carried out data extraction and then met to discuss and agree these findings. Reviews were grouped according to their aims and the two researchers developed themes from the review authors' findings.

A narrative synthesis approach was taken for the reviews of genotyping. The narrative was structured by review aim, with findings from each included review with similar aims discussed, in turn, and compiled by at least two members of the review team (GS, RW, HB).

Quality assurance

Two reviewers screened a subset of the same reviews using the inclusion/exclusion criteria until an inter-rater agreement >90% was attained. This was followed by single reviewer screening. Disagreements or queries on inclusion were referred to a third reviewer, as needed. The same process was applied during data extraction and risk of bias/quality assessment stages of the overview, with a second reviewer checking each review's data extraction and risk of bias/quality assessment. Quality assurance checks of data extraction and risk of bias assessment were conducted using a random sample of included reviews. The overview protocol was registered on PROSPERO. No changes were made to the protocol during the conduct of the overview, although findings for efficacy and safety were based on a single recent comprehensive high quality systematic review (Sterne et al. 2017) rather than an overview of multiple reviews.

Stakeholder involvement

The Department of Health and Social Care's Science, Research and Evidence Directorate and NHS England were consulted, as was a group of external academic and clinician advisors, with expertise in anticoagulation therapy who had worked previously with NHS England. In addition, to reduce the risk of duplicating the research effort of updating clinical guidelines in this research area, relevant teams at NICE were provided with the overview protocol.

4 Results: Flow of included reviews

A total of 3,119 references were located through searching. A total of 425 systematic reviews examining efficacy and/or safety were identified, precluding their analysis within the timelines set for this overview. One was a recently published NIHR HTA report of OACs efficacy and safety, and was determined to be the most comprehensive and highest quality for the purposes of this overview (Sterne et al. 2017); the other 424 were excluded. Of the remaining citations that were not focused on efficacy or safety, 49 were potentially relevant based on title and abstract and their full-text reports were retrieved (along with Sterne et al. 2017). After assessment of full-text reports a total of 23 reviews (including Sterne et al. 2017) were included in this overview. The flow of reviews through the overview process is listed in **Appendix 4**.

The review of efficacy and safety comprised multiple evidence syntheses concerning the range of UK-approved oral anticoagulant therapies. These are discussed in detail in Chapter 5. Another ten reviews examined genotyping and are described in Chapter 6. A further six reviews focused on self-monitoring and are discussed in Chapter 7. A total of nine reviews were identified that examined patients' and clinicians' perspectives about the issues related to utilisation and uptake of OACs and are reported in Chapter 8. Three of the included reviews were common to both self-monitoring and patient/clinician perspectives. As requested by the policy team, additional reference lists of reviews of economic evaluations and reviews of overdose or reversal treatments are provided in **Appendices 5** and **6**.

5 Results: Reviews of efficacy and safety of oral anticoagulant therapies

Summary of evidence reported in Sterne et al. (2017)

- Four systematic reviews with network meta-analyses (NMAs) of randomised controlled trials (RCTs) were conducted to identify the most effective, safe and cost-effective oral anticoagulants.

- The reviews covered four conditions or stages: Prevention of stroke in non-valvular atrial fibrillation (AF; Review 1); Primary prevention of venous thromboembolism (VTE) among those admitted to hospital and deemed to be at high risk (Review 2); Acute treatment of VTE (Review 3); and Secondary prevention of VTE (Review 4).

- Each review included RCTs of adults aged 18 years or older, who were eligible for oral anticoagulation.

- Interventions included warfarin, five novel oral anticoagulants (NOACs), including one that is not licensed in the UK,[15] low-molecular-weight heparin (LMWH) and antiplatelets (aspirin and/or clopidogrel).

- Outcomes measured included stroke, symptomatic VTE, symptomatic deep-vein thrombosis (DVT), symptomatic pulmonary embolism (PE), major, clinically relevant and intracranial bleeding, myocardial infarction, and death from all causes.

- RCTs were most often conducted in more than one centre, including some in multiple countries. Study locations were America, Europe, Asia, Australia, New Zealand, South Africa, Russia and Israel.

- Analyses were based on Bayesian fixed-effect models due to insufficient replication of intervention comparisons to allow estimation of the heterogeneity.[16] Investigation of potential moderators of effects (such as age and comorbidities) was, therefore, not possible in most cases.

- Reviews most often provided either direct-only evidence syntheses or indirect-only evidence syntheses for the NMAs. Where syntheses contained both direct and indirect comparisons and findings conflicted, the authors emphasised direct comparisons. All

[15] Apixaban (Eliquis®, Bristol-Myers Squibb, USA; Pfizer, USA), edoxaban (Lixiana®, Daiichi Sankyo, Japan), rivaroxaban (Xarelto®, Bayer HealthCare, Germany), dabigatran (Praxada®, Prazaxa®, Pradax®, Boehringer Ingelheim GmbH, Germany), as well as betrixaban (Portola Pharmaceuticals, San Francisco, CA, USA), which is not licensed in the UK. For licensed doses, see **Appendix 7**.
[16] For detailed information on analytic methods, see Sterne et al. (2017)'s report p50.

comparisons between different NOACs were based on indirect evidence derived from the networks (as there were no direct comparisons for these located in the literature).

- Rankogram analyses (the probability that each treatment is best, second best, and so on) and cost-effectiveness analyses were also reported (discussed below).

- The quality of each of the reviews presented by Sterne et al. (2017) was assessed using six domains[17] of the Cochrane Risk of Bias Tool, which categorises risk as 'low', 'high' or 'unclear' for each study. For each review, the AMSTAR risk of bias showed low risk in 11 domains,[18] high risk in two domains[19] and unclear in three domains.[20]

- Overall, the review authors rated the primary included studies as being at low risk of bias, although for the review on the prevention of stroke related to AF, the risk of bias was mixed (low, high and unclear) at the outcome level.

- No overlap between primary studies occurred, as each review examined specific topics.

Summary of findings

- Among AF populations, NOACs showed advantages over warfarin for most efficacy and safety outcomes. Of these, apixaban (5mg bd) offered the best balance between efficacy and safety and had the highest probability of being most cost-effective.

- There is no strong evidence to support the use NOACs for VTE for primary prevention (compared with low-molecular-weight heparin (LMWH)), acute treatment (compared with warfarin) and secondary prevention (compared with warfarin and aspirin).

- However, in terms of safety, apixaban (5mg bd) and rivaroxaban (15mg bd, then 20mg od) may reduce the risk of major and clinically relevant bleeding, compared with warfarin, for acute and secondary treatment and for secondary prevention of VTE.

[17] 1. Sequence generation; 2. Allocation concealment; 3. Blinding of participants and personnel; 4. Blinding of outcome assessment; 5. Incomplete outcome data; and 6. Selective reporting.
[18] Including use of PICO, inclusion criteria, duplicate screening, duplicate data extraction, description of included studies, risk of bias in RCTs, detail of funding arrangements, appropriate meta-analytic methods for RCTs, explored meta-analytic findings in light of risk of bias, discussed findings in light of heterogeneity, and reported conflicts of interests.
[19] Failed to report excluded studies and the justifications for their exclusion, and failed to test and discuss publication bias.
[20] Failed to provide a statement about following or deviating from the protocol, failed to conduct a comprehensive search strategy (not up to date), and the integration of risk of bias in the interpretation of the results was unclear.

- For secondary prevention of VTE, aspirin was likely to be the most cost-effective alternative to warfarin.

- authors concluded that prescribers and patients may choose to exercise caution when considering the results of these reviews. This was due to a lack of direct comparisons between NOACs, a reliance on short-term data, and limited generalisability to clinical contexts.

More detailed findings of the NMAs are provided below. Tabular details are provided in the appendices, including each review's key characteristics (**Appendices 8** and **9**) and their quality appraisal using AMSTAR criteria (**Appendix 10**).

Review 1. Prevention of stroke in AF

This review aimed to identify the most effective, safest and cost-effective oral anticoagulants to prevent stroke in AF. Forty-one papers detailing 23 RCTs carried out in primary care and anticoagulation clinics were included[21] (see **Appendix 8**). The size of studies varied widely, from 75 to 21,105 participants, with a total of 94,656 participants. All studies focussed on adults with non-valvular AF (including permanent or chronic, persistent, intermittent and paroxysmal). Mean age ranged from 63.3 to 81.5 years, and the percentage of men ranged from 44.9% to 82.9%.[22]

Warfarin was examined in all but two of the 23 studies, and was compared against a NOAC in 12 studies, and against aspirin in nine. Thirteen studies compared one NOAC each with warfarin (n=12) or aspirin (n=1). Edoxaban was the NOAC most commonly studied (n=4), followed by apixaban or dabigatran (n=3 each), rivaroxaban (n=2) and betrixaban[23] (n=1). The doses and frequencies of administration varied. The duration of treatment varied widely across trials, from three to 42 months. Mean time in therapeutic range (TTR) for warfarin ranged between 45.1% and 83%. NMAs were performed for seven outcomes: stroke or systemic embolism, ischaemic stroke, myocardial infarction (MI), major bleeding, clinically-relevant bleeding (CRB), intracranial bleeding and all-cause mortality. All trials provided data on stroke[24] and 15 measured myocardial infarction. Major bleeding and all-cause mortality (k=18 each) were the safety outcomes most frequently reported (see **Appendix 9**).

[21] Arms that were considered not to provide any evidence of interest to inform health decisions in the UK were excluded from the analyses by the primary review authors.
[22] Mean age was reported in only 61% of the trials, and percentage of males in 78%.
[23] Betrixaban is not licensed in the UK.
[24] More precisely, 15 trials assessed stroke or systemic embolism, and 13 measured ischaemic stroke.

The review authors Sterne et al. (2017) concluded that the primary studies were at low risk of bias. Two trials were at a low risk of bias for all six domains; 11 were at a high risk for one domain (all for blinding of participants and personnel); three were at a high risk for two or more domains (including blinding of participants/personnel, outcome assessments and allocation concealment). The remaining trials (k=7) were unclear for at least one domain (but had no high-risk domains). Grouping studies by each outcome, risk of bias was identified as 'mixed' (low, high and unclear ratings).

Findings and the risk of bias are summarised by outcome in **Appendix 12**. Rankogram analyses for warfarin (INR 2–3); dabigatran (150mg bd); edoxaban (60mg od); rivaroxaban (20mg od); apixaban (5mg bd); and antiplatelet therapy (≥ 150mg od), suggested that:

- Warfarin was ranked among the worst-performing drugs for risk of stroke or systemic embolism and ischaemic stroke, and was not among the best three anticoagulants for any of the outcomes
- Warfarin (INR 2–3) was ranked as the worst-performing for risk for intracranial bleeding
- With the exception of the CRB outcome, apixaban (5mg bd) was likely to be one of the best-performing for all outcomes (major bleeding, intracranial bleeding, all-cause mortality, stroke or systemic embolism, ischaemic stroke and MI) and had highest probability of being most cost-effective[25]
- Edoxaban (60mg od) was ranked second-best for reducing the risk of major bleeding and all-cause mortality (though there was evidence that edoxaban 30 and 60mg bd may increase that risk)
- With the exception of the all-cause mortality and MI outcomes, rivaroxaban (20mg od) was ranked lower in performance, compared with apixaban (5mg bd), dabigatran (150mg bd) and edoxaban (60mg od), across all outcomes
- Antiplatelet therapy (aspirin/clopidogrel ≥150mg od) was ranked among the lowest-performing for risk of stroke or systemic embolism and was not among the best three anticoagulants for any of the outcomes

Overall, in patients with AF, it was concluded:

- NOACs showed advantages over warfarin for most outcomes
- Among treatments in the rankogram analyses (warfarin (INR 2–3); dabigatran (150mg bd); edoxaban (60mg od); rivaroxaban (20mg od); apixaban (5mg bd); and antiplatelet therapy (≥ 150mg od)):
    - Warfarin and antiplatelet therapies were not ranked in the top three for any of the outcomes

[25] Antiplatelet (≥ 150mg od) therapy was not included in the cost-effectiveness analysis.

  - Apixaban (5mg bd) was likely to be one of the best anticoagulants for reducing the risk of stroke or systemic embolism, major bleeding, intracranial bleeding, all-cause mortality, stroke or systemic embolism, ischaemic stroke, and MI
- Apixaban also had the highest probability of being most cost-effective[25]

Review 2. Primary prevention of VTE

This review aimed to identify the most effective, safe and cost-effective oral anticoagulants for the primary prevention of VTE, in hospital settings. Forty-six articles detailing 43 RCTs were included.[26] However, only 38 RCTs were included in the analysis.[27] Adults considered to be at a high risk of VTE due to a medical condition (e.g., cancer, major trauma, or stroke) or surgery (hip or knee) were included. Of the 43 trials, 36 focused on patients who underwent a surgery; 18 for the hip, 17 for the knee, and one assessed both. The seven remaining studies assessed patients with a variety of medical conditions associated with a high risk of VTE.[28] Study size ranged from 67 to 8,323 participants, with a total of 77,563 participants overall. Where reported, mean age ranged from 41 to 76 years, and the percentage of men ranged from 13.1 to 62.7.[29]

Thirty-nine of the 43 studies assessed a LMWH.[30] Thirty-one compared one NOAC each with either LMWH (k=27), a placebo (k=3) or both LMWH and warfarin (k=1). Rivaroxaban was the NOAC that was most commonly studied (k=11), followed by dabigatran (k=7), apixaban and edoxaban (k=6 each) and betrixaban[31] (k=1). The doses and frequencies of administration varied. For the analyses, 'standard doses' of LMWH included tinzaparin (0.45mL od), enoxaparin (40mg od or 30mg bd) and dalteparin (5,000 IU). In the surgery trials, LMWH was started before the operation in 16 studies, after in 19, and one compared pre-op with post-op treatments. Overall, the duration of treatment varied from 4[32] to 182.6[33] days. None of the RCTs with warfarin reported the mean TTR.

NMAs were conducted for seven outcomes. Among the 43 papers, the most common efficacy outcome was symptomatic PE (k=35),[34] followed by symptomatic VTE (k=29) and

[26] Arms that were considered not to provide any evidence of interest to inform health decisions in the UK were excluded from the analyses by the primary review authors.
[27] Three trials were excluded from all NMAs because they used non-standard variants of heparin. No reference nor reasons for exclusion were provided for the two other trials. One of the latter was included in the assessment of major bleeding (39 studies were included for this outcome).
[28] Such as metastatic cancer, congestive heart failure, acute respiratory failure, infection (without septic shock), acute rheumatic disorder, or inflammatory bowel disease.
[29] Mean age and percentage of males were reported in 88% of trials.
[30] Standard dose for LMWH included tinzaparin (0.45mL od), enoxaparin (40mg od or 30mg bd) and dalteparin (5,000 IU).
[31] Betrixaban is not licensed in the UK.
[32] One trial provided LMWH for 3.3 to 11.3 days, and apixaban for 14.9 to 34.9 days.
[33] In three studies, the NOAC was given for a longer period than the comparator (LMWH).
[34] 30 trials were included in the analyses for PE, 28 for VTE, 20 for DVT, nine for MI, 34 for major bleeding, 25 for CRB, and 24 for mortality. No explanation was given for these differences in the numbers of trials included in the analyses.

symptomatic DVT (k=25), and these were analysed separately for medical conditions or type of surgery (hip or knee). The safety outcomes included major bleeding (k=39), all-cause mortality (k=28), CRB (k=27), and myocardial infarction (k=9), and these were assessed collectively across conditions.

Review authors (Sterne et al. (2017) judged the studies to be at a low risk of bias. Five trials were at a low risk of bias for all six domains, across all outcomes; eight were at a high risk for one or more domain (six for blinding of participants and personnel; one for blinding of outcome assessment, and allocation concealment; and one for blinding of participants and personnel, and incomplete outcome data). The remaining 30 were unclear for at least one domain, with none at high risk (some were at low risk across all domains for some outcomes, but not others). Blinding of participants and providers was a common issue for trials that had an open-label design (i.e. neither the participants nor the providers and assessors were blind to the treatment received). Similarly, by synthesis of outcome, risk of bias was also rated generally as low, but with some concerns.

Findings are summarised by outcome in **Appendix 13**.[35] Rankogram analyses for warfarin (INR 2–3); apixaban (2.5mg bd); dabigatran (220mg bd); rivaroxaban (10mg od); and LMWH post/pre-op (standard dose)[36] suggested that:

- Warfarin was likely to be the best intervention to reduce the risk of major bleeding events
- Rivaroxaban (10mg od) was likely to be one of the worst anticoagulants for major bleeding and CRB
- LMWH (post-op, standard dose) was likely to be the best or second-best intervention to reduce the risk of CRB
- Among AF populations, NOACs showed advantages over warfarin for most efficacy and safety outcomes. Of these, Apixaban (5mg bd) offered the best balance between efficacy and safety and had the highest probability of being most cost-effective
- There is no strong evidence to support the use NOACs for VTE for primary prevention (compared with low-molecular-weight heparin (LMWH), acute treatment (compared with warfarin) and secondary prevention (compared with warfarin and aspirin)
- However, in terms of safety, apixaban (5mg bd) and rivaroxaban (15mg bd, then 20mg od) may reduce the risk of major and clinically relevant bleeding compared with warfarin for acute and secondary treatment and secondary prevention of VTE
- For secondary prevention of VTE, aspirin was likely to be the most cost-effective alternative to warfarin

[35] Following Sterne et al. (2017), results for which the ratio between the limits of the 95% confidence intervals exceeded nine are not reported.
[36] Standard dose for LMWH included tinzaparin (0.45mL od), enoxaparin (40mg od or 30mg bd) and dalteparin (5,000 IU). Apixaban (2.5mg bd) and betrixaban (40mg od) were not included in the comparisons due to the lack of precision in their estimates.

Overall, for the primary prevention of VTE, Sterne et al. (2017) concluded:

- Neither the clinical effectiveness analysis nor the cost-effectiveness analysis (comparing dabigatran (220mg bd), rivaroxaban (10mg od), and apixaban (2.5mg bd), with LMWH (post-op, standard dose) as usual care) provided strong evidence that NOACs should replace LMWH for the primary prevention of VTE after hip or knee surgery
- Among treatments in the rankogram analyses (warfarin (INR 2–3); apixaban (2.5mg bd); dabigatran (220mg bd); rivaroxaban (10mg od); and LMWH post/pre-op (standard dose)), warfarin was likely to be the best to prevent major bleeding, and LMWH the best or second-best for CRB

Review 3. Acute treatment of VTE

The aim of Review 3 was to assess the most effective, safest and cost-effective oral anticoagulants for the acute treatment of VTE in hospital settings. Nine RCTs (referenced in ten papers) were included. The population consisted of adults with a new or recurrent objectively confirmed diagnosis of acute symptomatic VTE. Trial size ranged from 520 to 8,292, with a total of 28,803 patients. The mean age of patients ranged from 54.7 to 59.1 years, and the percentage of male patients ranged from 51 to 62**.** Four NOACs were assessed: rivaroxaban (n=4); dabigatran (n=2); apixaban (n=2); and edoxaban (n=1).

All nine trials compared the NOAC with warfarin. Trials lasted from 12 to 48 weeks, with assessments made at the end of the treatment period. Mean TTR ranged from 56.9% to 63.5% among the eight studies that measured it.[37] The outcomes that were assessed in the NMAs were symptomatic VTE (n=8),[38] symptomatic DVT (n=9), symptomatic PE (n=9), myocardial infarction (n=5), major bleeding (n=9), CRB (n=8), and all-cause mortality (n=8).

The trials were generally rated as at low risk of bias by Sterne et al. (2017). Three trials were at a low risk of bias for all six domains; four were at a high risk for one domain (blinding of participants and personnel) and one was at a high risk for two domains (blinding of participants and personnel and incomplete outcome data). One trial was at low risk across all domains for some outcomes, but not others. Similarly, by synthesis of outcome, risk of bias was rated as generally low.

Findings are summarised by outcome in **Appendix 14**. Rankogram analyses for warfarin (INR2-3), apixaban (5mg bd), dabigatran (150mg od), edoxaban (60mg or 30mg (17.6%) od) and rivaroxaban (15mg bd then 20mg od) suggested that:

- Warfarin had a high probability of being ranked worst for major bleeding and CRB

[37] Page 171 of Sterne's report mentions a range of 50.3% to 62.7%, but Table 107 shows values from 56.9% to 63.5%.
[38] Table 107 in Sterne's report shows eight studies, while the summary (p171) only mentions seven.

- Apixaban (5mg bd) had a high probability of being ranked best for major bleeding and CRB and of being ranked best, or second best, for symptomatic DVT, symptomatic VTE and all-cause mortality
- In the comparison of apixaban (5mg bd), dabigatran (150mg od), edoxaban (60mg or 30mg (17.6%) od), rivaroxaban (15mg bd then 20mg od) and warfarin (as usual care), apixaban (5mg bd) was the most cost-effective alternative to warfarin at willingness-to-pay thresholds of £20,000 to £30,000
- However, the reviewers concluded that further research on the relative efficacy and safety of apixaban, compared with other NOACs would increase the strength of evidence

Overall, in patients receiving acute treatment of VTE, the review authors (Sterne et al. (2017) concluded that:

- There was no clear evidence that NOACs or warfarin were more beneficial in terms of reducing symptomatic VTE, DVT or PE
- Apixaban (5mg bd) and rivaroxaban (15mg bd then 20mg od) may reduce the risk of major bleeding and CRB, compared with warfarin
- Apixaban (5mg bd) may reduce the risk of major bleeding, compared with some other NOACs (dabigatran 150mg od, edoxaban 60mg or 30mg (17.6%) od, and rivaroxaban 15mg bd then 20mg od)
- Apixaban (5mg bd) was likely to be the most cost-effective alternative to warfarin, although more research into the relative efficacy and safety of apixaban compared with other NOACs is needed

Review 4. Secondary prevention of VTE

The aim of Review 4 was to assess the most effective, safest and most cost-effective oral anticoagulants for the secondary prevention of venous thromboembolic disease. Ten RCTs (reported in 11 articles), examining interventions in primary care and anticoagulation clinics, were included.[39] Adults who had completed a minimum of three months of anticoagulant therapy for objectively confirmed, first VTE (DVT and/or PE), without recurrence, were included. Trial size ranged from 162 to 2,866, with a total of 10,390 patients. The mean age ranged from 53 to 67.3 years, and the percentage of males from 52.8 to 63.9.[40]

Three NOACs were assessed; dabigatran (150mg bd) (n=2), apixaban (2.5 and 5mg bd) (n=1), and rivaroxaban (20mg od) (n=1). Three trials compared the NOAC with placebo and one compared dabigatran with warfarin. Four trials compared warfarin with placebo (n=2) or no

[39] Arms that were considered not to provide any evidence of interest to inform health decisions in the UK were excluded from the analyses by the primary review authors.
[40] Mean age was reported in 90% of trials, and percentage of males in all of them.

treatment (n=2), and two compared aspirin (100mg od) and placebo. Studies lasted from 3 to 51.6 months. Mean TTR was reported in three of the five warfarin trials ranging from 64% to 81%. Seven outcomes were assessed in the NMAs including symptomatic VTE (n=10); symptomatic DVT (n=9); symptomatic PE (n=9); myocardial infarction (n=5); major bleeding (n=10); CRB (n=6); and all-cause mortality (n=9).

The trials were generally rated as at low risk of bias by Sterne et al. (2017). Three trials were at a low risk of bias for all six domains; two were at a high risk for one domain (blinding of participants and personnel); and one was at a high risk for two domains (blinding and allocation concealment). The remaining four were a combination of low risk and unclear risk of bias. Similarly, by synthesis of outcome, risk of bias was also rated generally as low, but with some concerns.

Findings are summarised by outcome in **Appendix 15**.[41] Rankogram analyses could not be performed due to the substantial proportion of imprecise estimates. Overall, for the secondary prevention of VTE using warfarin and NOACs, Sterne and colleagues concluded:

- There was no clear evidence of differences between NOACs and warfarin, and between the different NOACs for symptomatic VTE and DVT
- For symptomatic PE, the risk was higher with apixaban (2.5mg bd) than warfarin, and lower with dabigatran (150mg bd) and rivaroxaban (20mg od) than apixaban (2.5mg bd)
- For major or clinically relevant bleeding, the risks were higher with warfarin, dabigatran (150mg od) and rivaroxaban (20mg od), than with placebo. However, compared with warfarin, the risk of these outcomes was lower for dabigatran (150mg bd) and apixaban (2.5mg and 5mg bd)
- For major bleeding and CRB, the risk was higher with dabigatran (150mg bd) and rivaroxaban (20mg od) than apixaban (2.5mg bd and 5mg bd)
- Warfarin and NOACs (apixaban 2.5mg and 5mg bd; dabigatran 150mg bd; and rivaroxaban 20mg od) reduced the risks of VTE and DVT, compared with aspirin

In the comparison of aspirin, warfarin, apixaban (2.5 and 5), dabigatran, and rivaroxaban, with no treatment, aspirin was likely to be the most cost-effective alternative to warfarin at willingness-to-pay thresholds of £20,000 and £30,000 per QALY, although there was uncertainty about whether or not it was more cost-effective than no treatment. It was not cost-effective to prescribe NOACs or warfarin. The reviewers concluded that more research, comparing the cost-effectiveness of aspirin and no pharmacotherapy, would be beneficial.

Quality appraisal of the four reviews with AMSTAR

[41] Results for which the limits of the 95% confidence intervals exceeded nine were excluded from synthesis of indirect effects (due to imprecision).

As shown in **Appendix 10**, the quality of reviews was rated using AMSTAR criteria (Shea et al. 2007). The risk of bias was judged to be low across 11 domains. Two domains showed high risk of bias; one because the reviews did not present information on the excluded studies, and one for not testing nor discussing potential publication bias.

The risk of bias was unclear for three domains (transparency between report and protocol, search strategy, and discussion of findings in light of risk of bias). A protocol was registered for each review, but there was no indication as to whether these protocols were followed integrally or modified. In terms of the searches, whilst comprehensive, they were last updated 2.5 years before the publication of the report (a maximum of a two-year gap between search and publication date is required for a low risk on AMSTAR). Lastly, whilst the review authors (Sterne et al. 2017)'s analysis of risk of bias was very comprehensive, there was little integration of these assessments into the review conclusions about the efficacy and safety of anticoagulants.

6 Results: Reviews of genotyping

Summary of evidence

- Ten reviews were assessed in this synthesis. Within these reviews, 50% or more of the 58 included primary studies assessed populations which included those with AF and/or VTE.

- However, the outcomes that were reported in these studies were estimated from mixed patient populations, i.e. populations which comprised AF and/or VTE alongside patients with other indications for warfarin use.

- Because the data of the AF/VTE population could not be extracted from the mixed-population data presented in the reviews, none of the studies met our overview's original inclusion criteria. Of the 22 identified reviews that focused on genotyping, four were not systematic reviews, six did not include AF or VTE patient populations, one did not focus specifically on anticoagulation and one did not have any information on health or cost outcomes.

- Despite this, it was felt that the remaining reviews have value and highlight some of the clinical implications of genotyping within this patient population. We have, therefore, produced a descriptive synthesis of the identified research.

- Genotyping was examined in different ways:
    - Six reviews looked at how clinical outcomes differed between patients who received genotype-guided dosing, compared with those who received non-genotype-guided dosing, such as those using clinical dosing algorithms;
    - Three reviews investigated how warfarin maintenance doses differed between patients with different gene polymorphisms;
    - One review investigated how adverse outcomes differed between patients with different gene polymorphisms; and
    - Three of the reviews investigated how ethnicity may play a role in the variation observed in anticoagulant dosing and clinical outcomes between patients.

- The reviews investigated polymorphisms of four main genes CYP4F2, the VKORC1, the CYP2C9 and the Apolipoprotein E (ApoE).

- The assessed reviews included total populations ranging from 1,766 to 5,688 patients who had at least one indication for the use of anticoagulation therapy.

- Reviews included, Asian, Caucasian, African American and Hispanic patients; however, ethnicity was not always clearly reported (e.g., 'White' or 'Black' populations); and

included studies varied in their proportions of male and female patients, ranging from 12.6% to 70% female participants.

- The most common clinical outcome assessed was the time within therapeutic range (TTR), assessed in six of the ten reviews. Other clinical outcomes included an international normalised ratio (INR) > 4, time to maintenance dose and adverse events, namely minor and major bleeding and thrombolytic events.

- Seven of the reviews included only randomised controlled trials. One review included case-control and cohort studies and another included prospective clinical trials. Finally, one review provided insufficient information to determine which study designs were included.

- Quality appraisal of the reviews (AMSTAR) showed a low risk of bias across five domains,[42] moderate risk of bias across six domains[43] and high risk of bias in the remaining seven domains.[44]

- Of the included reviews, 50% focused primarily on the same eight primary studies, indicating a high degree of overlap.

Introduction

This systematic overview assessed the use of genotyping in oral anticoagulant therapy for stroke prevention in atrial fibrillation (AF) or acute treatment and primary and secondary prevention of venous thromboembolism (VTE).

Patients who are prescribed anticoagulants, commonly warfarin, for these conditions take the medication on a daily basis as the drug has a narrow 'therapeutic window' or period of time in which the drug is effective (Xu et al. 2014). Warfarin and other anticoagulants are broken down in the body and particular genes can affect the rate at which this occurs. The rate at which warfarin is broken down in the body varies between patients, therefore the dose of warfarin prescribed must be tailored to individuals. Knowing a patient's 'genotype', or which particular genes are present, can help to determine the optimal daily dose of anticoagulant required for the specific patient (Dean 2012).

[42] Including use of: PICO, duplicate data extraction, description of included studies, appropriate meta-analytic methods for RCTs, discussion of heterogeneity, publication bias and conflict of interest statements.
[43] Failed to report/provide: specified inclusion criteria, risk of bias assessment for RCTs/NRCTs, appropriate meta-analysis methods, and the impact of risk of bias on meta-analysis or in the interpretations on results.
[44] Publication of a protocol, comprehensive search strategy, reported duplicate screening, list of excluded studies, and funding arrangements.

Findings

Ten reviews assessed the use of genotyping in oral anticoagulant therapy (Chen et al. 2016; Dahal et al. 2015; Franchini et al. 2014; Goulding et al. 2015; Jin et al. 2014; Shi et al. 2015; Sun et al. 2016; Tang et al. 2015; Xu et al. 2014; Yu et al. 2016). The characteristics of these reviews are reported in **Appendices 16** and **17**. A list of 22 reviews of genotyping excluded at full text screening is provided in **Appendix 20**.

Our inclusion criteria required that for any review to be included, 50% or more of the included studies had to be related to AF and/or VTE populations. As the reviews identified in this synthesis did not report results separately for AF and VTE patients, but instead reported, in the reviews, results from mixed patient populations, e.g., those with AF, VTE and other indications for warfarin use, such as heart valve disease, none of the studies met our original inclusion criteria. The baseline risk of developing a particular outcome, for example, a thrombolytic event will differ between populations of patients with different conditions. Furthermore, some outcomes differ in definition between conditions; for example, the INR used to determine the therapeutic range of an anticoagulant varies between conditions being treated (Chen et al. 2016). The data for AF/VTE populations could not be extracted from the mixed-population data presented in the reviews. Consequently, there is uncertainty that the outcomes are generalisable to AF/VTE patients in the UK who are prescribed anticoagulants for stroke prevention.

The evidence, however, from these reviews does hold value and highlights some of the clinical implications of genotyping within the AF and or VTE patient populations, as well as providing evidence related to the role of patient ethnicity in genotype-guided dosing. Therefore, what follows is a descriptive synthesis, of the reviews published from 2014 onwards, that assesses the use of genotyping in oral anticoagulant therapy.

Characteristics of included reviews

Of the included reviews, four considered the role of ethnicity in genotype-guided dosing (Chen et al. 2016; Jin et al. 2014; Sun et al. 2016; Yu et al. 2016). The reviews investigated inter-ethnic variation in dose requirement i.e. the impact of gene polymorphisms on anticoagulant dose requirements in Caucasian, Asian and African populations. This type of information could be relevant in a UK setting, as a country with a growing multi-ethnic population.

The main gene polymorphisms considered in the included reviews were those of the genes:

- CYP4F2 assessed in six of the ten reviews (Chen et al. 2016; Dahal et al. 2015; Goulding et al. 2015; Shi et al. 2015; Sun et al. 2016; Xu et al. 2014);
- VKORC1 assessed in six of the ten reviews (Dahal et al. 2015; Franchini et al. 2014; Goulding et al. 2015; Jin et al. 2014; Shi et al. 2015; Xu et al. 2014);
- CYP2C9 assessed in six of the ten reviews (Dahal et al. 2015; Franchini et al. 2014; Goulding et al. 2015; Shi et al. 2015; Tang et al. 2015; Xu et al. 2014); and

- Apolipoprotein E (ApoE) assessed in one review (Yu et al. 2016).

Goulding et al. (2015) also included studies that looked at the genotypes of HLA-B*5701, HIV anti-retroviral resistance mutations, TMPT, CYP2C19 and CYP3A5.

The reviews included patient populations with a wide variety of indications for anticoagulant medication including patients with AF, VTE, PE, cardiomyopathy, trans-ischemic attack, heart value replacement (HVR), deep-vein thrombosis (DVT), prosthetic value replacement, stroke, rheumatic heart disease and valvular heart disease.

Review aims

Broadly, the reviews had two main aims. The first was to identify how clinical outcomes differed between patients who received anticoagulant dosing which was genotype-guided, compared with those who received standard clinical dosing (Dahal et al. 2015; Franchini et al. 2014; Goulding et al. 2015; Shi et al. 2015; Tang et al. 2015; Xu et al. 2014). The clinical outcomes were mainly time within therapeutic range (TTR) and adverse events, such as minor or major bleeding. The second main aim was to determine how warfarin maintenance dose differed between patients with different gene polymorphisms (Jin et al. 2014; Sun et al. 2016; Yu et al. 2016). These reviews typically looked at the mean difference in warfarin dose as the primary outcome. Finally, one review also investigated how adverse outcomes differed between patients with different gene polymorphisms (Chen et al. 2016).

Reviews of genotype-guided dosing

Dahal et al. (2015) aimed to compare genotype-guided dosing with standard dosing in adult patients with various indications for warfarin use. Ten RCTs (2,505 patients in total) were included, of which nine included AF/VTE populations. Warfarin doses ranged from 2.5-10mg/day (where specified), and included studies testing CYP2C9, CYP4F2 and VKORC1. The studies' populations included 0 to 100% White, 0 to 35%, Black and 0 to 100% Asian participants, with average ages ranging from 41.6 to 70.5 years. The majority of participants were male; 44.6 to 70% of studies' participants were female. The countries in which the studies were based were not reported. The review's primary outcome was percentage time in therapeutic range (TTR). Secondary outcomes were major bleeding, time to maintenance dose, supra-therapeutic INR of >4, thromboembolism, non-major bleeding and all-cause mortality. Studies' follow-ups ranged from 0.5 to six months.

Franchini et al. (2014) aimed to assess whether or not genotype-guided and standard dosing resulted in different rates of clinically relevant events. Nine RCTs (2,812 patients in total) were included in the review, all of which included AF/VTE populations. All but one study focused on warfarin; one other focused on acenocoumarol and phenprocoumon and the review looked at the CYP2C9 and VKORC1 gene polymorphisms. Mean/median age ranged from 41 to 70 years, with 65 to 100% of White ethnicity and 36 to 58% female. The countries in which the studies were based were not reported. The review's primary outcomes were incidence of major bleeding, thrombosis and death. Secondary outcomes were time to reach

a therapeutic INR, percentage of TTR, time to reach a stable dose, percentage time spent at sub-therapeutic INR and number of days in hospital. Studies' follow-ups ranged from 22 to 90 days.

Goulding et al. (2015) explored whether genotype-guided prescribing reduced adverse drug events (ADEs) and improved drug treatment responses. Fifteen RCTs (5,688 patients in total) were included in the review, of which eight included AF/VTE populations. Studies included patients from a clinical setting taking warfarin, acenocoumarol/phenprocoumon, tacrolimus (immunosuppressant for post organ transplant, interleukin-2 inhibitor), clopidogrel/prasugrel/azathioprine (antiplatelet drugs), antiretroviral agents or abacavir and looked at CYP2C29, VKORC1, CYP4F2, HLA-B*5701, CYP2C19, CYP3A5, TMPT and HIV anti-retroviral resistance mutations. Populations were ethnically diverse, ranging from 0 to 100% Caucasian, 0 to 100% Chinese, 0 to 27% Black and unspecified proportions of Hispanic participants. Mean/median ages ranged between 41 and 70 years. Seventeen to 69% of the participants were female. Studies were conducted in 19 countries, including Canada, China, France, Greece, Israel, The Netherlands, Sweden, UK, and the USA. Outcomes included percentage time in therapeutic international normalised ratio range and adverse drug events such as haemorrhage and thrombosis. Follow-ups ranged from seven days to four months.

Shi et al. (2015) assessed whether genotype-guided warfarin dosing can improve clinical outcomes in comparison to conventional dosing. Eleven RCTs (2,678 patients in total) were included in the review, of which eight included AF/VTE adult populations. Studies were conducted in the USA, China, Israel, UK and Sweden. The review focused on warfarin and looked at CYP2C9, VKORC1 and CYP4F2. The ethnicity and gender of studies' participants was not reported. The median age was 59.7 years. The review's primary outcome was TTR; secondary outcomes were INR greater than 4, time to maintenance dose and the first target INR, adverse events during anticoagulation treatment, frequency of major bleeding, thromboembolic events and death from any cause. Follow-ups ranged from 28 days to three months.

Tang et al. (2015) aimed to determine whether genotype-guided dosing of coumarin anticoagulants did not improve the percentage time in the therapeutic INR range. Eight RCTs (1,805 patients in total) were included in the review, of which seven included AF/VTE adult populations. Studies were conducted in Europe, Asia and the USA. The review focused on coumarin anticoagulants and looked at VKORC1 and CYP2C9. Mean age ranged from 41.6 to 70.5 years and 12 to 70% were female. Ethnicity was not reported. The primary outcome was the mean difference in percentage time within the therapeutic INR range. Secondary outcomes were major bleeding events, thromboembolic events, and INR at or greater than four events. Follow-ups ranged from 28 to 90 days.

Xu et al. (2014) assessed whether genotype-guided pharmacogenetic dosing of warfarin is superior to clinical dosing. Eight RCTs (2,098 patients in total) were included in the review,

of which seven included AF/VTE adult populations. Study locations were not reported. The review focused on warfarin, with doses ranging between 5 and 10mg, and looked at CYP2C9, VKORC1 and CYP4F2 polymorphisms. The age, gender and ethnicity of populations were not reported. The primary outcome was time within the therapeutic range; secondary outcomes were major and minor bleeding, thromboembolic events and INR ≥4. Follow-ups ranged from 28 to 90 days.

Reviews of genotype influence on maintenance dosage

Jin et al. (2014) estimated the impact of VKORC1-1639G>A genetic polymorphism upon warfarin dose requirement. Thirty-two prospective clinical trials (5,005 patients in total) were included, of which 25 included AF/VTE adult populations. The review focused on warfarin and looked at the VKORC1-1639G>A polymorphism. Study populations included Caucasian, Asian or African ethnicities, with mean ages from 36.0 to 86.7 years; 12.6 to 64.9% of studies' participants were female. Studies were conducted in 16 countries: Brazil, Canada, China, Egypt, France, India, Iran, Japan, Korea, Lithuania, Malaysia, Morocco, Sudan, Turkey, UK, and the USA. The primary outcome was weighted mean maintenance dose of warfarin. Follow-up durations were not specified.

Sun et al. (2016) aimed to investigate the impact of the CYP4F2 polymorphism on warfarin dose requirements. Twenty-two studies (4,549 patients in total) were included, of which 11 included AF/VTE adult populations. The review focused on warfarin, with doses ranging from 2.51 to 22.52mg/day and looked at CYP4F2 polymorphism. The majority of the studies' populations were Chinese (n=16), with two studies of Japanese populations and one each of Indian, Turkish, Korean and Asian. The majority of participants, 53.5%, were female; their age was not reported. The review assessed mean difference in daily warfarin dose. Follow-up durations were not reported.

Yu et al. (2016) assessed the impact of APOE alleles on mean daily warfarin dose. Nine RCTs (1,766 patients in total) were included, all of which included AF/VTE adult populations. Studies were conducted in Brazil, China, Egypt, India, Malaysia, Sweden, UK and the USA. The review focused on warfarin and looked at Apolipoprotein E (ApoE). The studies' populations were Caucasian, Asian and/or African-American, with ages ranging from 42.3 to 71 years; 34.6 to 65.5% were female. The review assessed the warfarin dose associated with each genotype. The duration of follow-ups was not reported.

Reviews of genotypes and adverse outcomes

One review also investigated how adverse outcomes differed between patients with different gene polymorphisms. **Chen et al. (2016)** evaluated the impact of the CYP4F2 polymorphism on bleeding complications and over-anticoagulation due to coumarin. Eight case-control and cohort studies (3,101 patients) were included, of which seven included AF/VTE adult patient populations. Studies were published between 2008 and 2014. The review focused on warfarin and acenocoumarol, with doses ranging from 3 to 7mg per day.

The studies' populations included Caucasian, Asian and African-American participants. Their average ages ranged from 4.8 [sic] to 66 years; 41.0 to 54.7% of studies' participants were female. The countries in which the studies were based were not reported. The review assessed total haemorrhage, major haemorrhage, INR<4 and over-anticoagulation. Studies' follow-ups ranged from three to 45 months.

Quality of included reviews

Quality appraisal of the reviews (AMSTAR) showed a low risk of bias across five domains (PICO, duplicate data extraction, description of included studies, appropriate meta analytic methods for RCTs, discussion of heterogeneity, publication bias and conflict of interest statements). The included studies demonstrated a moderate risk of bias across six domains in that they failed to report or provide clear information on the following: specified inclusion criteria, risk of bias assessment for RCTs/NRCTs, appropriate meta-analysis methods, the impact of risk of bias on meta-analysis or in the interpretations of results. There was a high risk of bias in the remaining seven domains. These focused on the publication of protocols, comprehensive search strategy, reported duplicate screening, list of excluded studies and funding arrangements. Quality assessment ratings are shown in **Appendix 18**.

Overlap of primary studies included in the reviews

A total of 58 primary studies that focused on AF and VTE were included in the ten reviews. Overlap in primary studies on AF and VTE was noticeable but was not consistent across included reviews. Five of the ten reviews focused primarily on the same eight primary studies (Dahal et al. 2015; Franchini et al. 2014; Shi et al. 2015; Tang et al. 2015; Xu et al. 2014). These primary studies were: Anderson et al. 2007; Borgman et al. 2012; Burmester et al. 2011; Hillman et al. 2005; Jonas et al. 2013; Kimmel et al. 2013; Pirmohamed et al. 2013; and Sconce et al. 2005. However, the remaining five reviews drew on a variety of other primary studies. Details are provided in **Appendix 19**.

7 Results: Reviews of self-monitoring

Summary of evidence

- Six reviews were included in this synthesis, which covered five types of self-monitoring interventions; education only (n=1), education plus patient decision aid (to inform preferences for anticoagulation therapy) (n=1), self-testing with guidance on dosing from a clinician) (n=3), self-management (n=2) (self-testing and treatment according to an algorithm), and pharmacist-managed anticoagulation (warfarin) therapy (PMWT)[45] (n=3).[46]

- Time in therapeutic range (TTR) and proportion of international normalised ratio (INR) in range were used to assess effectiveness.

- One review focused exclusively on participants with AF, one on participants predominately with AF and/or VTE and the remaining four reported data from participants with a range of conditions that included AF/VTE populations. Of the mixed populations, data for participants with AF could be isolated in two reviews. No reviews reported data exclusively on populations with VTE.

- Four reviews exclusively examined RCTs; the remaining two included both RCTs and non-RCTs.

- Two reviews focused exclusively on warfarin; the rest included more than one type of oral anticoagulant.

- Only one review rated the trials within the review as being of high quality; another graded the evidence as being of moderate quality; and in two reviews the trials were mostly rated as low quality. In another two reviews, whilst risk of bias was conducted, the results were not interpreted nor applied to the findings, leading to uncertainty about the quality of these reviews' conclusions.

[45] Although pharmacist management may not strictly be self-management, it can be easier to access for patients and could reduce pressure on GP or specialist services, and is, therefore, included here in self-monitoring.
[46] Some reviews assessed more than one intervention, so these numbers do not add up to six.

- AMSTAR quality appraisal of the reviews showed a low risk of bias across seven domains,[47] moderate risk of bias across six domains[48] and high risk of bias in the remaining three domains.[49]

- Percentage of overlap in trials across reviews is calculated by intervention synthesis (0% for educational interventions, 0 to 100% for self-testing, 63 to 100% for self-management and 31% for pharmacist managed therapy) (see **Appendices 22** and **25** for more details)

Summary of findings

Overall, among participants with AF, low-quality and limited evidence suggests:

- **Education only and education plus patient decision aids** might improve anticoagulation management, compared with usual care.

- **Self-testing** may be as effective as usual care but does not offer enhancements over and above usual care.

- **Self-management** might improve the quality of anticoagulation management, compared with usual care.

Overall, among mixed populations (including but not limited to AF and/or VTE), evidence from low- and moderate-quality studies suggests:

- **Self-testing** interventions may improve the INR values in therapeutic range, compared with usual care. However, for the TTR outcome, using the Rosendaal interpolation method, findings were mixed, with both positive (longer) and negative (shorter) time in therapeutic range for the **self-testing** intervention, compared with usual care.

- **Self-management** interventions had both positive (higher) and negative (lower) effects for **INR numbers** in therapeutic range, and positive (longer) and negative (shorter) effects for time in therapeutic range, compared with usual care. Low-quality meta-analytic evidence indicated that **self-management may be** as effective

[47] Including use of PICO, duplicate screening, duplicate data extraction, description of included studies, risk of bias RCTs/nRCTs, appropriate meta-analytic methods for RCTs/nRCTs.
[48] Failed to: report conflict of interests; detail funding arrangements; explore meta-analytic findings in light of risk of bias; discuss findings in light of heterogeneity; provide study protocol or statement about deviations from it; provide a list of excluded studies.
[49] Failed to: specify inclusion criteria, search strategy, and examine publication bias.

as usual care, but does not offer enhancements over and above usual care, in terms of TTR.

Overall, among mixed populations (including but not limited to AF and/or VTE) mixed-quality evidence (high risk and uncertain) suggests:

- Pharmacist-managed anticoagulation may improve TTR, assessed using the Rosendaal interpolation method, compared with usual care.

A more in-depth synthesis of the findings is reported below and summarised in **Appendix 22**. This details the size of effects, their direction and associated statistical information. Findings are organised by type of intervention.

Intervention types

Education, and Education and Decision aids

Only one review examined the impact of education or education and decision aids on anticoagulant therapy effectiveness. **Clarkesmith et al. (2017)** built on their original review, first published in 2013 (Clarkesmith et al. 2013a), with updated searches in 2016. The review evaluated the effects of education, education and decision aids, or self-management plus education (the latter reported in the section below on self-monitoring), compared with usual care, among adults with AF who were eligible for, or currently receiving, oral anticoagulant therapy (OAT). Twenty articles reporting on 11 randomised controlled trials (RCTs) were included with a total of 2,246 patients, aged between 59 and 75 years. Time in therapeutic range or INR values in range were reported in six trials. The percentage of time in therapeutic range (TTR), using the Rosendaal et al. (1993) method was reported in four trials (Christensen et al. 2007; Clarkesmith et al. 2013b; Gadisseur et al. 2003; Vormfelde et al. 2014). In one trial the TTR was reported in days (Voller et al. 2005) and one reported the percentage of INRs in range (McAlister et al. 2005). Follow-ups ranged from three to 12 months.

Most of the studies included in the systematic reviews were conducted in Europe (five), and one was in Canada (McAlister et al. 2005). Ethnicity data were tabularised for individual studies, where reported (see Characteristics of included studies, in Clarkesmith et al. (2017), begins p38), but were not referred to or summarised by the primary review authors.[50] Two of the interventions were conducted in a hospital or anticoagulation clinic setting (Christensen et al. 2007; Clarkesmith et al. 2013b; Gadisseur et al. 2003) and two of the trials were in general practices (McAlister et al. 2005; Vormfelde et al. 2014). The trials referred to the use of oral anticoagulation therapy (OAT) in general, rather than named drugs. Quality was assessed using the Cochrane 'Risk of Bias' tool (Higgins and Green 2011)

[50] The characteristics of the self-management studies are discussed here for simplicity, but the results of the self-management trials are discussed below in the section on self-management.

and the GRADE Working Group grades of evidence (Grade Working Group 2004). The evidence was categorised as being very low to low in quality, across different outcomes, based on the limitations of the individual studies, mainly due to the absence of information about the allocation concealment procedure or blinding and incomplete outcome data (attrition bias).

Three of the included trials that compared education only with usual care reported percentage TTR (Clarkesmith et al. 2013b; Gadisseur et al. 2003; Vormfelde et al. 2014), though these data were not comparable and were, therefore, not combined in a quantitative synthesis.[51] Clarkesmith et al. (2013b) found significantly higher percentage TTR in the education intervention group (median 76.2%, interquartile range (IQR) 64.1% to 97.3%), compared with the usual care group (median 71.3%, IQR 51.2% to 84.7%), at six months among an AF population, and although the direction of effects remained the same at 12 months (median 76.0%, IQR 60.5% to 85.0% versus median 70.0%, IQR 62.0% to 79.0%, respectively), the difference did not obtain statistical significance. Vormfelde et al. (2014) found that the percentage TTR was significantly higher in the education intervention group (comprising a 20-minute video presentation, an eight-page brochure, and a corresponding questionnaire) (mean 69%, SD 25.1%), compared with the brochure only group (mean 64%, 28.2%), at six months, among the AF population (unpublished data).

McAlister et al. (2005) examined the effectiveness of a general education session plus patient decision aid to help clarify personal values regarding desired outcomes and preferences for therapy, preferred role in the decision process and any questions for their physician. Based on the percentage of INR values in range, McAlister et al. (2005) found that, compared with usual care, INR management improved in the intervention arm (p=0.020; INRs were between 2.0 and 3.0 on 72% of the days at three months versus 65% at baseline, in the intervention group, and 66% of the days at three months versus 70% of the days at baseline, in the control group). Nonetheless, at 12-month follow-up, INR control in both arms had returned to baseline levels.

Overall, there appears to be some weak evidence to support the beneficial effects of education, and education plus patient decision aid, on TTR, at least in the short term. The lack of longer-term effects indicates that booster sessions may be helpful. Clarkesmith et al. (2017) concluded that the effect of self-monitoring plus education on INR values was uncertain, compared with usual care, due to the very low quality of the evidence and the likelihood that further high-quality trials may affect these results.

[51] Gadisseur et al. (2003) had provided unpublished data on the AF cohort for the three arms of the trial. However, due to a typo in the report, it is not possible to establish which data belonged to which intervention group, thus these data are not summarised here. The authors were contacted, but a reply was not received before the point of submission.

Self-monitoring: Self-testing and or self-management interventions

Three reviews examined the impact of self-monitoring: Clarkesmith et al. (2017), Sharma et al. (2015) and Heneghan et al. (2016). The **Clarkesmith et al. (2017)** review (introduced in the section above on education) assessed three trials that examined the impact of **self-management** plus education among AF populations (Christensen et al. 2007; Gadisseur et al. 2003; Voller et al. 2005). Two of these studies measured percentage TTR using the Rosendaal et al. (1993) method of calculation (Christensen et al. 2007; Gadisseur et al. 2003) and were, therefore, pooled, using fixed-effect meta-analysis. The results showed that **self-management** plus education, whilst in a positive direction, did not statistically significantly improve TTR when compared with usual care (MD 6.3%, 95% CI -5.63% to 18.25%, I^2=0%, 2 trials, 69 participants, very low-quality evidence). Voller et al. (2005) reported the cumulative percentage of time in INR, rather than TTR using the Rosendaal et al. (1993) method. Time in INR (mean 67.8%, SD 17.6%) was higher in the **self-management** group, compared with usual care (mean 58.5%, SD 19.8%) (no statistical tests were reported).

Sharma et al. (2015) examined the effectiveness of self-monitoring of coagulation status in people receiving long-term vitamin K antagonist therapy, compared with standard clinic or GP care, in people with different clinical conditions. Twenty-six RCTs (8,763 participants), reported in 45 articles, were included. The majority of trials were conducted in Europe (n=22); three trials were conducted in Canada, and one in the USA. The self-monitoring intervention included both **self-testing** (**self-testing**, with guidance on dosing from a clinician) and **self-management** (**self-testing** and treatment according to an algorithm). The majority of the included trials (22/26) used the CoaguChek system for INR monitoring.[52] Of the included trials, only two exclusively recruited participants with AF and both evaluated the CoaguChek system (Khan et al. 2004; Voller et al. 2005). The remaining trials targeted participants with heart valve disease (n=6) or participants with mixed diagnoses (including AF and heart valve disease, n=15; three were unspecified). Only one of the included trials targeted children (in mixed group), and across the included adult-based trials, participant age ranged from 16 to 91 years. Warfarin was received by participants in 14 trials (12 in mixed group) and was the most common anticoagulation drug reported. In seven trials, participants were taking phenprocoumon and/or acenocoumarol and/or fluindione (six in mixed group) and, in one trial, participants received either warfarin or phenprocoumon. In the remaining four trials (two in mixed group) the type of vitamin K antagonist therapy was unspecified.

The time that INR was in the therapeutic range was reported in 18 trials, and the INR values reported in therapeutic range was measured in 12 trials. The length of follow-up ranged

[52] Two trials used either INRatio or the CoaguChek S, for INR measurement (but did not present results according to the type of the point-of-care device used), while the other two trials used the ProTime system.

from 14 weeks[53] to more than 4 years. Nine trials reported follow-ups ≥ 12 months, and the type of standard care encompassed anticoagulation clinic (n=15),[54] GP/physician (n=6), and anticoagulation clinic or GP/physician (n=5). Overall, the quality of the trials was generally low with only four trials judged to be at a low risk of bias. The majority of trials were judged to be at an 'unclear' or 'high' risk of bias.

For the UK-based trial (Khan et al. 2004) that sampled participants with AF, whilst INR time in therapeutic range was higher in the **self-testing** intervention (mean % = 71.1; SD=14.5), compared with control (mean % = 70.4, SD=24.5), the difference was modest and did not reach statistical significance. The results for the Germany-based trial (Voller et al. 2005) were included within the Clarkesmith et al. (2017) review and are, therefore, already discussed above. However, Sharma et al. (2015) included statistical tests for the INR time outcome (Clarkesmith et al. (2017) did not report these) and, additionally, reported INR value data for this trial. Consistent with Clarkesmith et al. (2017), INR time in therapeutic range was higher for the self-management intervention (mean cumulative days = 178.8 (SD=126)), compared with control (mean = 155.9 (SD=118.4)), albeit not statistically significantly. For the INR value in target range outcome there was a statistically significant effect (p=0.0061) favouring the **self-management** intervention: INR values in the intervention group were 67.8% (SD=17.6), versus 58.5% in the control group (SD=19.8). Nonetheless, Voller et al. (2005)'s study was identified as having a high risk of bias and in Khan et al. (2004) the risk of bias was categorised as unclear.

Collectively, for the studies that measured INR time in the therapeutic range, in 15 of the 18 trials, the values were higher among participants receiving the self-monitoring (either **self-testing** or **self-management**) intervention, compared with participants in standard care (three obtained statistical significance, p<0.001). A pooled synthesis of five trials was possible for **self-testing** interventions[55] (including Khan et al. 2004, but not Voller et al. 2005). Results showed a modest but significantly higher percentage of **INR time** in therapeutic range, (weighted mean difference (WMD) 4.44, 95% CI 1.71 to 7.18; p=0.001). A pooled synthesis of six trials was possible for **self-management**, compared with standard care. The results showed that a very modest difference was observed favouring intervention for the INR time outcome, although this effect was not statistically significant (WMD 0.47, 95% CI –1.40 to 2.34; p=0.62).

Variation in the measures used to assess INR values in therapeutic range prevented the pooling of data across trials for this outcome. Narrative synthesis showed that the INR values in therapeutic range were reported in eight trials that assessed AF or mixed indications. For

[53] There was a discrepancy between the text (p15), which reported a range from 14 weeks to 4 years, and Table 31, which reported that follow-up in the Menendez-Jandula et al. (2005) study ranged from 0.3 to 16.9 months.
[54] Professional testing in clinic (13) or self-testing in clinic (2), which was compared with self-management.
[55] Includes AF and HVD exclusive populations, and mixed indications.

the **self-testing** intervention, of the two trials that assessed this outcome, both reported better percentages of INR values in therapeutic range compared with control, and one was statistically significant ($p<0.001$). For **self-management**, five of the seven trials reported a higher percentage of INR values in the therapeutic range, than with usual care, and two of these were statistically significant ($p<0.05$).

Overall, there is little evidence that **self-monitoring** (**self-testing/self-management**) of vitamin K antagonist therapy is more effective than standard clinic care, among populations with AF, in terms of TTR and INR values reported in therapeutic range. Among mixed-diagnoses groups (i.e. those with a combination of AF, VTE and other conditions), there is some low-quality evidence to suggest that **self-testing** and **self-management** improve the percentage of TTR and INR values, compared with standard care, albeit modestly for the TTR outcome. The extent to which the groups with mixed diagnoses sampled patients with AF or heart valve disease was not reported and, therefore, requires clarification.

Heneghan et al. (2016) updated their initial review (Garcia-Alamino et al. 2010), with searches conducted in November 2013 and July 2015.This led to the identification of an additional 10 trials for inclusion. A total of 27 included articles provided data on 28 RCTs (with a total of 8,950 participants)[56] that were published between 1989 and 2013. Most of the trials were conducted in Europe (five in the UK, five in Germany, three in the Netherlands, three in Denmark, one in Ireland, one in France, one in Spain and one in Austria); seven were from the United States and Canada; and one was from Australia.

Few trials focused exclusively on AF. Two trials exclusively sampled participants with atrial fibrillation (Khan et al. 2004; Voller et al. 2005);[57] and 20 included people on long-term anticoagulation for any indication. Six included only those on oral anticoagulants after mechanical valve replacement (Azarnoush et al. 2011; Horstkotte et al. 1998; Kortke et al. 2001; Sidhu and O'Kane 2001; Soliman Hamad et al. 2009; Thompson et al. 2013).

A range of oral anticoagulants was evaluated. In most studies, the oral anticoagulant tested was usually warfarin (15 trials) followed by phenprocoumon or acenocoumarol (three trials); phenprocoumon (two trials) and warfarin or acenocoumarol (one trial). The type of oral anticoagulant was not reported in six trials. The range of settings for the intervention varied. Eleven trials were in a primary care setting, 13 trials were in specialist anticoagulation clinics; three were in either setting, and one trial used data from a medical

[56] One article (Gadisseur et al. 2003) contained data on two trials that compared self-monitoring or self-management of oral anticoagulation, with standard care. There were discrepancies in the numbers reported in the review, as there were 28 articles, describing 29 trials, if you include Gadisseur et al. (2003) as two trials.

[57] Summarised in Clarkesmith et al. (2017) and Sharma et al. (2015), therefore, not reported again here. Note that, like in Clarkesmith et al. (2017), Heneghan et al. (2016) only report the cumulative days outcome from Voller et al. 2005, and not the values in range outcome.

analysis laboratory. These settings correspond to the type of usual care which was used as a control.

Trial follow-up ranged from two months (White et al. 1989) to 57 months (Matchar et al. 2010). Overall, the available evidence was judged to be moderate according to GRADE (Grade Working Group 2004). The main flaw (related to the TTR outcome) was the absence of information on allocation concealment or blinding.

The effects of the intervention varied across studies. In terms of TTR (15 trials with AF or mixed populations), according to the table of results[58] (Heneghan et al. 2016, Additional tables, Table 1, pp80-81), three trials reported a statistically significant difference ($p<0.01$) between the intervention and control groups (Beyth et al. 2000, Christensen et al. 2011, Matchar et al. 2010).[59] This difference ranged from -4[60] (Matchar et al. 2010; 66.2% control, 62.4% intervention) to +24 (Beyth et al. 2000; 32% control, 56% intervention) percentage points, assuming that we correctly assigned the appropriate columns to intervention and control, as these were not labelled.[61] Two differences were in a negative direction[60] (control out-performed the intervention) and one was positive (i.e., the intervention group out-performed the control). Of the remaining trials, five differences were negative (favoured control) and seven were positive (Rasmussen et al. 2012 had two arms, with two different decision tools; one found no difference).

In 12 trials, the intervention was **self-testing**, in 15 trials it was **self-management**, and in one trial both interventions were assessed (Gadisseur et al. 2003). Fifteen trials[62] (11 trials with AF or mixed populations) reported the percentage of **INR values** in the target range, overall (percentage of overall tests in range) or for each individual (percentage of tests for each individual in range), however, pooling of the results was not possible due to heterogeneity in the measures of INR.[63]

Results[64] showed that for the **self-testing** interventions**,** three trials were in a positive direction (longer TTR, one statistically significant) and four in a negative direction (shorter

[58] Note that the findings reported in the text (Heneghan et al. 2016, p16) differed from those in the table (Heneghan et al. 2016, Additional tables, Table 1). Here, we have reported the findings from the table, and noted any discrepancies in the footnotes.
[59] The authors also referenced Siebenhofer et al. (2007) as statistically significant ($p<0.029$), the significance level was not reported in the text; this had a positive effect (+9).
[60] Reported as positive in the text (p16).
[61] The authors were contacted for clarification, but we did not receive a response in time for this publication.
[62] Four of these (Horstkotte et al. 1998, Sidhu and O'Kane 2001, Kortke et al. 2001, Soliman Hamad et al. 2009) only assessed patients with heart valve replacements.
[63] The mean percentage of tests in range was reported as either the percentage of tests overall or the percentage of tests for each individual.
[64] According to the table of results (Heneghan et al. 2016, Additional tables, Table 1, pp80-81), assuming that we correctly assigned the appropriate columns to intervention and control, as these

TTR, two statistically significant) compared with usual care.[65] For the same outcome, results showed that for the **self-management** interventions, five were in a positive direction (longer TTR, one statistically significant) and three were in a negative direction (shorter TTR, all not statistically significant) compared with usual care.

In terms of the 11 trials reporting **INR values** in target range (11 trials with AF or mixed populations), two were **self-testing** interventions and eight were **self-management** interventions. According to the table of results (Heneghan et al. 2016, Additional tables, Table 1, pp80-81), with the exception of one **self-management** intervention (Grunau et al. 2011; 82.4 control, 80.2 intervention; -2)[66] the remaining ten trials assessing **INR value** in target range showed higher percentages in the intervention group compared with usual care (five statistically significant, $p<0.05$).

In summary, results of the Heneghan et al. 2016 review for the **TTR** outcome were mixed for the trials sampling AF or mixed populations, with approximately equal numbers of trials reporting successful and unsuccessful interventions, for both type of self-monitoring interventions (**self-testing** and **self-management**). For the eleven studies assessing mean percentage of **INR values** in target range, the results were more consistently in favour of the intervention which was predominately **self-management** (assessed in eight studies).[67]

Pharmacist-managed interventions

Three reviews assessed the effectiveness of pharmacist-managed interventions: Manzoor et al. (2017), Entezari-Maleki et al. (2016) and Zhou et al. (2016).

Manzoor et al. (2017) conducted a systematic review to evaluate the quality of warfarin anticoagulation control in outpatient pharmacist-managed anticoagulation services (PMAS) compared with routine medical care (RMC). Twenty-five studies met the inclusion criteria. Of these, three were RCTs and 22 were non-randomised controlled studies. A total of 12,252 participants were included across studies with a mean age that ranged from 47.4 to 81.0 years. The majority of patients were treated for AF or VTE (including DVT and PE) (n=23 of 25, 92.0%). Gender was not recorded and only seven studies reported race/ethnicity (mainly Caucasian, n=4; Malay, n=2; Qatari, n=1). In terms of the country, most of the studies were carried out in the United States (n=13), followed by Asia (n=4); Canada (n=3), United Kingdom (n=2) and others (one each in Spain, Qatar, and New Zealand).

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were not labelled. The authors were contacted for clarification, but we did not receive a response in time for this publication.

[65] GP management, hospital anticoagulation service, anticoagulation clinic

[66] This was also reported to be positive in the text (p16), whereas Kaatz et al. (unpublished data; see Kaatz et al. 2001) was reported to be negative (unfavourable to the intervention).

[67] The results in the text of Heneghan et al. (2016)'s report differed from those in the table, particularly for TTR, for which the results were much more favourable in the text. The results were more consistent for the percentage of values in range, but this lack of consistency casts some doubt on all the conclusions of the review. Without checking each individual paper's results, the directions of the effects, and the conclusions, cannot be relied upon.

Whilst most of the studies (n=19 of 25, 76.0%) used the linear interpolation approach to determine TTR, meta-analysis across studies was not conducted due to variation in measurements of TTR. Follow-ups ranged from three months to four years, with the highest proportion of studies having a follow-up ≥18 months (n=10 of 25, 40.0%). Individual study quality was assessed using the Downs and Black checklist (Downs and Black 1998). Results showed that the mean ± SD Down's score was 19.5 ± 5.7, (range 16 to 28). Because the authors did not provide any guidance on how the Downs and Black checklist should be interpreted, nor any other comments on study quality, there is uncertainty about the quality of the primary studies included in the review.

Overall, a higher TTR was reported in the PMAS group, compared with RMC, in the majority of the studies (n=23, including two of the three RCTs). Of these 23 studies, 19 (83.0%) reported a statistically significant result for TTR (including two of the three RCTs), indicating that the quality of anticoagulation control was better in the PMAS group, compared with control. This improvement in TTR ranged from 1.7% to 28.0% in the PMAS group, relative to control, and 16 studies (69.6%) showed a larger improvement in TTR than 7%. Manzoor et al. (2017) concluded that pharmacist-managed outpatient-based anticoagulation services attained better quality of anticoagulation control, compared with routine care. Variation in the levels of improvement may be due to the various settings and countries in which the studies took place. Furthermore, due to the uncertainty about the quality of the individual studies, these findings should be interpreted cautiously.

Entezari-Maleki et al. (2016) conducted a systematic review to evaluate the quality of warfarin anticoagulation control in outpatient pharmacist-managed warfarin therapy (PMWT) compared with usual medical care. Twenty-four studies met the inclusion criteria. Of these, four were RCTs and 20 were observational studies. In total, 11,607 participants were included across studies (summary statistics for age, gender and ethnicity were not reported). The majority of patients were treated for AF, deep vein thrombosis, pulmonary thromboembolism, or valvular heart diseases (relative proportions not reported). In terms of the country, most of the studies were carried out in the USA (n=12), followed by Canada (n=6), and the United Kingdom (n=4).[68] One study was conducted in Spain and one in Australia. Three RCTs and five observational studies reported on TTR by the Rosendaal et al. (1993) method. For these studies reporting the TTR outcome, follow-up ranged from three to six months among the RCTs and between at least two months and 17 months among the observational studies. Individual study quality was assessed using the Downs and Black checklist (Downs and Black 1998). RCTs were additionally assessed using the Jadad scale (Oxford scale).

Among the studies that included TTR by the Rosendaal et al. (1993) method, the Downs and Black score ranged between 21 and 29 for the RCTs, and between 15 and 22 for the

[68] Figures extracted from table 2 in Entezari-Maleki et al. (2016) as they differed to the figures reported in the text.

observational studies. It was also reported that the Jadad scale for RCTs was scored 3 as a high-quality RCT, although it is unclear what this meant. Unfortunately, the authors did not provide any guidance on how the Downs and Black checklist should be interpreted, nor provide any other comments on study quality, thus there is some uncertainty about the quality of the observational studies reviewed.

Data, pooled (but not weighted) using the three RCTs, showed that percentage of time in the therapeutic range (TTR) was longer in the PMWT group (84.3%, ±3.2%), compared with in the UMC groups, (82.2%, ±8.7%), though the findings did not obtain statistical significance (95% CI -26.3% to 30.5%, p=0.781). Among the observational studies (n=5), TTR was statistically significantly higher for PMWT, when compared with UMC (72.1% ±7.7% v. 56.7% ±7.6%; 95% CI 4.2% to 26.6%; p=0.013).

Overall, whilst those receiving pharmacist-managed Warfarin therapy attained better quality of anticoagulation control, compared with routine care, among the lower quality non-randomised studies, the difference among the more robust RCTs, whilst favouring PMWT, was small and not statistically significant. Furthermore, due to the uncertainty about the quality of the individual studies, these findings should be interpreted cautiously.

Zhou et al. (2016) conducted a systematic review to evaluate the quality of pharmacist-managed warfarin, compared with other models of care. Eight RCTs were included with a total of 1,493 patients. However, only four trials (comprising 646 participants) reported the percentage of time within the standard therapeutic range (INR 2.5 ±0.5) and within the expanded therapeutic range (INR 2.5 ±0.7) using the Rosendaal et al. (1993) interpolation method for TTR.

All four relevant trials reported sampling patients with mixed indications that included two or more of the following diagnoses: AF, DVT, PE, mechanical valve replacement (MVR), MI, stroke, cardiomyopathy and others (unspecified) (relative proportions of each not reported).

Control groups varied and included usual care (n=1), physician managed (n=2) and one labelled as PCP but not defined. Across studies, age ranged from 57.7 to 70 years and gender from 51.2% to 68.4% male. Ethnicity data were not reported. Three of the studies were conducted in Canada and one was conducted in Canada and one in the UK. Follow-up ranged from three to six months. Risk of bias in the individual studies was assessed using the Cochrane Risk of Bias tool and GRADE (Grade Working Group 2004).

Meta-analysis of the four RCTs showed that the percentage of time within the standard therapeutic range was longer in the pharmacist-managed care, compared with other models (mean difference = 3.66, 95% CI 2.20 to 5.11; p<0.00001, high-quality evidence), without heterogeneity. For the percentage of time within the expanded therapeutic range, whilst the pharmacist-managed group increased time in range, compared with other models, the

difference did not obtain statistical significance (MD 2.85, 95% CI -0.56 to 6.26; p=0.10, moderate-quality evidence), with heterogeneity.

Overall those receiving pharmacist-managed Warfarin therapy attained better quality of anticoagulation control, compared with other models, in trials rated as being of moderate-(due to heterogeneity) to-high quality.

AMSTAR risk of bias assessment

As shown in **Appendix 24**, the AMSTAR quality appraisal of the reviews showed a low risk of bias across seven domains (including use of PICO, duplicate screening, duplicate data extraction, description of included studies, risk of bias assessment for RCTs/nRCTs and appropriate meta-analytic methods for RCTs/nRCTs). Moderate risk of bias was reported across six domains (due to the absence of a study protocol or statements about deviations from it, information on potential conflict of interests, funding arrangements, links between meta-analytic findings with risk of bias assessments, discussion of heterogeneity, and a list of excluded studies). A high risk of bias was coded for the remaining three domains (including specification of inclusion criteria, search strategy, and examination of publication bias).

Summary

Overall, there appears to be some low-quality evidence to support the beneficial effects of **education** (based on two RCTs) and **education plus patient decision aid** among participants with AF (based on one RCT) on TTR (using the Rosendaal et al. (1993) method), though the lack of long-term effects indicates that booster sessions may be helpful.

Only two reviews examined **self-testing** interventions using an AF population (Sharma et al. 2015; Heneghan et al. 2016) and one study (Khan et al. 2004), with uncertain quality, was identified for inclusion. Results indicated that there was little evidence to support the effectiveness of **self-testing** on improving time in INR, compared with usual care, but it did not perform worse.

In terms of **self-management**, exclusively within AF populations, only three primary studies were located (Voller et al. 2005; Christensen et al. 2007; Gadisseur et al. 2003) across three reviews (Sharma et al. 2015; Clarkesmith et al. 2017; Heneghan et al. 2016).[69] Results indicate that there was low-quality evidence suggesting that, **self-management may** improve TTR compared with usual care. However, two reviews identified a high risk of bias in the relevant trials (Clarkesmith et al. 2017 and Sharma et al. 2015) therefore, the effect of **self-management** on TTR, compared with usual care, is uncertain, especially given the few studies that had examined this research question.

[69] Voller et al. (2005) was assessed in all three reviews, whereas Christensen et al. (2007) and Gadisseur et al. (2003) were synthesised only by Clarkesmith et al. (2017), who obtained unpublished data from the primary authors.

Overall, in light of the few studies that focus exclusively on AF populations, reliable conclusions about the impact of self-monitoring interventions on this patient population cannot be drawn.

Among mixed-diagnoses groups, the low-to-moderate quality evidence suggests that **self-testing** interventions may improve the INR numbers in therapeutic range, compared with usual care. However, for the TTR outcome, findings from moderate-quality evidence were more mixed, with both positive (longer) and negative (shorter) time in therapeutic range for the **self-testing** intervention compared with usual care.

For the **Self-management** interventions, the evidence was mixed for types of outcomes, with both higher and lower INR numbers in therapeutic range, and shorter and longer time in therapeutic range, compared with usual care. Low-quality meta-analytic evidence indicated that **self-management may** be as effective as usual care but does not offer enhancements over and above usual care, in terms of TTR. The variation in findings indicates the presence of potential moderators operating.

The evidence for pharmacist-managed anticoagulation (from mixed-quality studies rated as high and uncertain) was more consistent across the reviews indicating that pharmacist-managed anticoagulation may improve TTR, compared with usual care, among mixed-diagnoses groups. There were no reviews evaluating pharmacist-managed anticoagulation services exclusively in populations with AF and none of the interventions were exclusively examined in populations with VTE.

8 Results: Reviews of stakeholder perspectives

Summary of evidence

- Nine reviews met our inclusion criteria and were included in this synthesis. All of the reviews included studies that examined atrial fibrillation (AF) patients; five reviews focused on AF patients only, and four examined a range of conditions that included venous thromboembolism (VTE).

- Most reviews focused on general populations receiving VKA or oral anticoagulants (OACs) therapy, with only one review focused specifically on NOACs adherence and satisfaction amongst renal patients. The number of studies included across the reviews ranged from three to 140; where reported, between 341 and 7,295 people participated.

- Four reviews examined factors influencing the optimal use of warfarin in AF; three of these additionally looked at the role of NOACs in optimising OAC use. These reviews included a wide range of primary study designs, including systematic reviews, trials, observational studies, and patient data registries and guidelines.

- Two reviews examined the preferences and values of patients toward VKA use and NOAC use, including discrete-choice experiment studies and other economic evaluations.

- Three reviews examined patient satisfaction and/or adherence within evaluations of either educational/behavioural interventions or pharmacist-managed therapy.

- While all nine reviews examined data from patients, only one included studies which examined patients' experiences directly using qualitative methods. This review also sought qualitative studies of physicians' perspectives.

- The quality of studies was assessed using eleven domains[70] of the Joanna Briggs Institute (JBI) Quality Assessment Tool, which determines whether the domain was 'met' or 'not met/unclear' for each study. Across all reviews, the JBI quality

[70] 1. Clearly stated review question; 2. Appropriate inclusion criteria; 3. Appropriate search strategy; 4. Adequate sources searched; 5. Appropriate critical appraisal criteria; 6. Dual independent critical appraisal; 7. Methods to minimise data extraction errors; 8. Appropriate methods to combine studies; 9. Assessed publication bias; 10. Data supported recommendations; 11. Appropriate new research recommendations made.

assessment showed five domains were low risk,[71] four domains were moderate risk[72] and two domains were high risk.[73]

- The reviews were determined to be of moderate-to-high quality; however, the quality of included primary studies varied, where authors conducted quality assessment. Most reviews lacked assessment of publication bias or could have errors in data extraction.

- A total of 159 primary studies were included across the nine reviews. Of these, 23 primary studies (39%) contributed findings to more than one review. However, only three were included in more than two reviews, suggesting a limited amount of overlap.

Summary of findings

- Drug efficacy matters most to patients and physicians, followed next by safety (i.e. risk of bleeding); but after efficacy and safety, no clear patterns emerge about which 'convenience attributes' or factors involved in daily management are most important to facilitate patient adherence.

- Beyond efficacy and safety, a wide range of factors influence patients' decisions on initiating, switching or continuing OACs therapy; little evidence was located to suggest which factors are more important for different groups during each of these decision points.

- The need for, lack of, or inaccurate knowledge influences patients' decisions about initiating or continuing therapy; and one review of educational and behavioural interventions suggested these can have a small but significant positive effect on quality of life anxiety and depression sub-scale measures.

- Patients are also influenced by previous experience of stroke, bleeding and/or therapy, and by the experiences and support of their families.

- Clinicians draw on rapidly evolving scientific knowledge, their knowledge of the patient, and their clinical experiences; however clinical management can be complicated by the involvement of, and communications with, other professionals.

[71] All included reviews met: clear review question; appropriate inclusion criteria; appropriate search strategy; adequate sources searched; data supported recommendations.
[72] Three reviews failed to report appropriate criteria for appraising studies and dual critical appraisal; two reviews failed to report appropriate methods to combine studies; one review failed to make appropriate directives for new research.
[73] Six reviews failed to minimise errors in data extraction; eight reviews failed to assess for publication bias.

- Decisions about initiating or maintaining OACs therapy may depend on the extent to which patients and clinicians feel the responsibility for deciding is their own or is shared; a review of decision-aid interventions suggested that patients report higher decision conflict with their use and did not significantly affect patients' satisfaction with their physician consultation.

- Patients and clinicians indicated that improvements were needed in how information about OACs therapy was communicated during the clinical encounter.

- Patients reported a need for ongoing support and information from providers when deciding and managing OACs therapy; reviews of pharmacist-led interventions suggest patients may be more satisfied with this support than usual care.

General findings

Nine systematic reviews examined stakeholder issues related to the utilisation and uptake of OACs Alamneh et al. 2016, Clarkesmith et al. 2017, Entezari-Maleki et al. 2016, Loewen et al. 2017, Mas Dalmau et al. 2017, Pandya and Bajorek 2017, Wilke et al. 2017, Willett and Morrill 2017, Zhou et al. 2016. The characteristics and findings of each review are presented in **Appendix 26**. All of the reviews included studies that examined AF patients; five reviews examined AF alone Alamneh et al. 2016, Clarkesmith et al. 2017, Loewen et al. 2017, Mas Dalmau et al. 2017, Pandya and Bajorek 2017. The remainder examined a range of conditions that included VTE. Reviews of stakeholder perspectives did not focus on specific populations of patients beyond the conditions of AF or VTE, with one exception: one review focused specifically on NOACs adherence and satisfaction amongst renal patients Willett and Morrill 2017.

Four reviews examined the factors influencing the overuse/underuse/optimal use of warfarin in AF, using diverse methods Alamneh et al. 2016, Mas Dalmau et al. 2017, Pandya and Bajorek 2017, Willett and Morrill 2017. Two of these included systematic reviews, meta-analyses, guidelines, trials and non-experimental research Alamneh et al. 2016, Willett and Morrill 2017. The other two reviews sought data from studies of patients and physicians using qualitative and mixed methods Mas Dalmau et al. 2017, Pandya and Bajorek 2017. Another two reviews examined the preferences and values of patients toward the use of VKAs and NOACs, including discrete-choice experiment studies and other economic evaluation designs Loewen et al. 2017, Wilke et al. 2017. Finally, three reviews examined patient satisfaction and/or adherence through evaluations that either examined RCTs of educational/behavioural interventions Clarkesmith et al. 2017 or pharmacist-managed therapy evaluated in RCTs only Zhou et al. 2016 or via RCTs and non-RCTs Entezari-Maleki et al. 2016.

The number of studies included across the reviews ranged from three to 140. Only five of the nine included reviews provided data concerning the number of participants Clarkesmith et al. 2017, Loewen et al. 2017, Mas Dalmau et al. 2017, Pandya and Bajorek 2017, Wilke et al. 2017. Here, the review authors reported that between 341 and 7,295 people participated in the included studies.

Overall, the quality assessment of included reviews was moderate to high. Using the Joanna Briggs Institute review quality rating criteria, most reviews failed to assess publication bias and/or did not take steps to minimise errors in data extraction. The ratings for individual quality characteristics used in the JBI tool are presented for each review in **Appendix 27**.

Data from a total of 159 primary studies within the nine reviews were included in this overview. These are shown in **Appendix 28**. Of these, 23 primary studies contributed findings to more than one review. This represents a 39% overlap of primary studies across the reviews Pollock et al. 2017. Only three of these 23 overlapping primary studies were included in more than two reviews, suggesting a limited amount of overlap.

Review summaries

The aims of the included reviews suggest three distinct areas in which factors examining prescribing, utilisation and uptake were described:

- reviews examining factors related to overuse or underuse of OACs,
- reviews seeking to understand patient preferences and values, and
- reviews of interventions which included measures of decision-making, adherence, quality of life or satisfaction.

Each of these types of review will be discussed in turn below.

Reviews examining perceptions and attitudes about factors related to OAC over/underuse

A total of four reviews examined patients' and physicians' perceptions and attitudes toward OACs therapy. **Alamneh et al. (2016)** aimed to evaluate current use, overuse and underuse of OACs in AF, and the current features of adoption patterns of NOAC use. A total of 140 primary studies were included. The number of participants was unclear. Study designs were both prospective and retrospective and included observational studies, reviews, meta-analyses, RCTs and published AF treatment guidelines. The review met seven of 11 quality criteria upon assessment. Review authors primarily reported current use patterns for OACs, but in terms of factors influencing this only noted that TTR rates were higher in North America (50.9%) and western Europe (62.4%), while varying between 32% and 40% in India, China, Southeast Asia and Africa (Oldgren et al. 2014). Reasons for this variation were not provided. Regarding NOAC use, review authors noted concerns with the lack of a reversal agent and the risks of not remembering to take NOACs without the reminder of regular blood

monitoring tests. Broad availability and practice-related integration of NOACs were suggested to be limited, prompting review authors to suggest that these factors may be related to poor compliance with guidelines on OAC therapy.

Mas Dalmau et al. (2017) sought to understand patients' and physicians' perceptions and attitudes about the barriers and facilitators of VKA use, to explore the factors associated with its underuse. A total of nine qualitative or mixed-methods studies reported on the views of 250 AF patients and 91 physicians. Review authors synthesised three themes related to VKA use that were experienced by patients and clinicians: the information needed to reinforce coagulation use, the balance of advantages and disadvantages of VKAs, and roles in decision-making and therapy management. Review authors identified a further three patient-specific themes: the need for information and understanding, the impact of therapy on daily life, and factors influencing their satisfaction with therapy.

Pandya et al. (2017) sought to understand the factors underpinning patients' acceptance of and decision to use anticoagulant therapy in order to explain OAC non-adherence in patients with AF, and to what extent NOACs might address these factors given that NOACs may address some issues but create others. A total of 48 studies were included, comprised predominantly of surveys, interviews and one discrete-choice experiment with 4,151 patient participants. This review met seven of 11 quality criteria upon assessment. Review authors reported a range of factors influencing adherence to warfarin and/or NOACs, organised into five main categories. These included therapy-related factors, patient-related factors, factors specific to the disease, socioeconomic factors, and health system-related factors.

Willett and Morrill (2017) aimed to describe patient adherence and satisfaction in the use of NOACs amongst renal patients, as a specific population for whom this evidence was needed. Review authors reported ten included studies but only cited nine, which included systematic reviews, meta-analyses, trials and surveys involving an unknown number of participants with AF and/or VTE. The review met five of 11 quality criteria on assessment. Review authors noted that after establishing the safety and efficacy of NOACs in renal-impaired patients, patient preferences should also be considered. These included costs, dosing frequency, monitoring, and dietary interactions.

Reviews examining patient preferences and choices

Two systematic reviews examined patient preferences and values in relation to warfarin and/or NOACs. **Loewen et al. (2017)** aimed to provide insights into the values and preferences of AF patients for stroke prevention therapy, as well as the specific factors that influences those values and preferences. This was undertaken to try and explain previously identified heterogeneity in values and preferences for antithrombotic therapy (MacLean et al. 2012), while also focusing on AF. Examining discrete-choice experiments, standard gamble, time/probability trade-off, qualitative, conjoint analysis, questionnaires and scenario ranking methods amongst patients requiring antithrombotic therapy in AF, a total of 25 studies were included with 641 participants. Some of these examined values in relation

with warfarin alone, some examined warfarin compared with aspirin, and others evaluated warfarin versus NOAC preferences. Quality assessment of this review was high: 10 of 11 quality criteria were achieved. Review authors noted a wide variation in the attributes of antithrombotic therapy most valued by patients, suggesting a need for tailored provision of information.

Wilke et al. (2017) aimed to review the preferences of AF patients when deciding on an OAC treatment, including both warfarin and NOACs. Comprising 26 included studies of 7,295 patients and 266 physicians, this review included discrete-choice analysis, trade-off studies, gamble techniques, analytical hierarchy methods and traditional conjoint analysis. Some included studies also incorporated physician surveys. This review was considered to be of high quality, meeting 9 out of 11 quality criteria. Findings suggested that patients across studies were more willing to accept a higher risk of bleeding if a drug could achieve a certain threshold risk of reducing stroke; however, the threshold varied across studies. Further, no other factors were prioritised above each other when considering warfarin or NOACs, also patients preferred once daily administration with no dietary or drug interactions, no need for bridging therapy and no blood control monitoring.

Reviews of intervention studies reporting factors related to uptake

Three systematic reviews reported factors related to uptake. **Clarkesmith et al. (2017)** aimed to evaluate the effects of educational and behavioural interventions for OAT on TTR patients with AF. Examining randomised controlled trials, a total of 11 studies were included examining 2,246 participants. The trials and their effects were compared with usual care, the types of interventions included; *educational* (booklets, videos, self-management and decision aids) and *behavioural*: CBT, self-monitoring, motivational interviewing, heart rate variability and biofeedback. Quality assessment of this review was high: 10 of 11 quality criteria were achieved. Review authors concluded that there was inadequate evidence to draw conclusions regarding the impact of educational or behavioural interventions on TTR in AF patients: based on two trials of low-quality evidence, involving 587 participants in total, the findings suggested small but positive effects of education on anxiety measures in a HADS quality of life outcome (MD -0.62, 95% CI -1.21 to -0.04) and depression (MD -0.74, 95% CI -1.34 to -0.14), compared with usual care, over 12 months. Educational interventions centred on patient information included: educational booklets; video as media for additional information; self-management interventions (such as INR self-monitoring), which also educated patients on decision aids and talking interventions. The behavioural interventions included techniques that attempted to modify patients' behaviour towards treatment and symptoms, such as: cognitive behaviour therapy (CBT); self-monitoring or management interventions that included significant educational components; motivational interviewing and heart rate variability biofeedback. Patient satisfaction was reported as a secondary outcome with only four trials and one education intervention. The single education intervention did not provide any AF-specific data. Finally, the use of the decision aids did not significantly affect patients' satisfaction with their physician consultation.

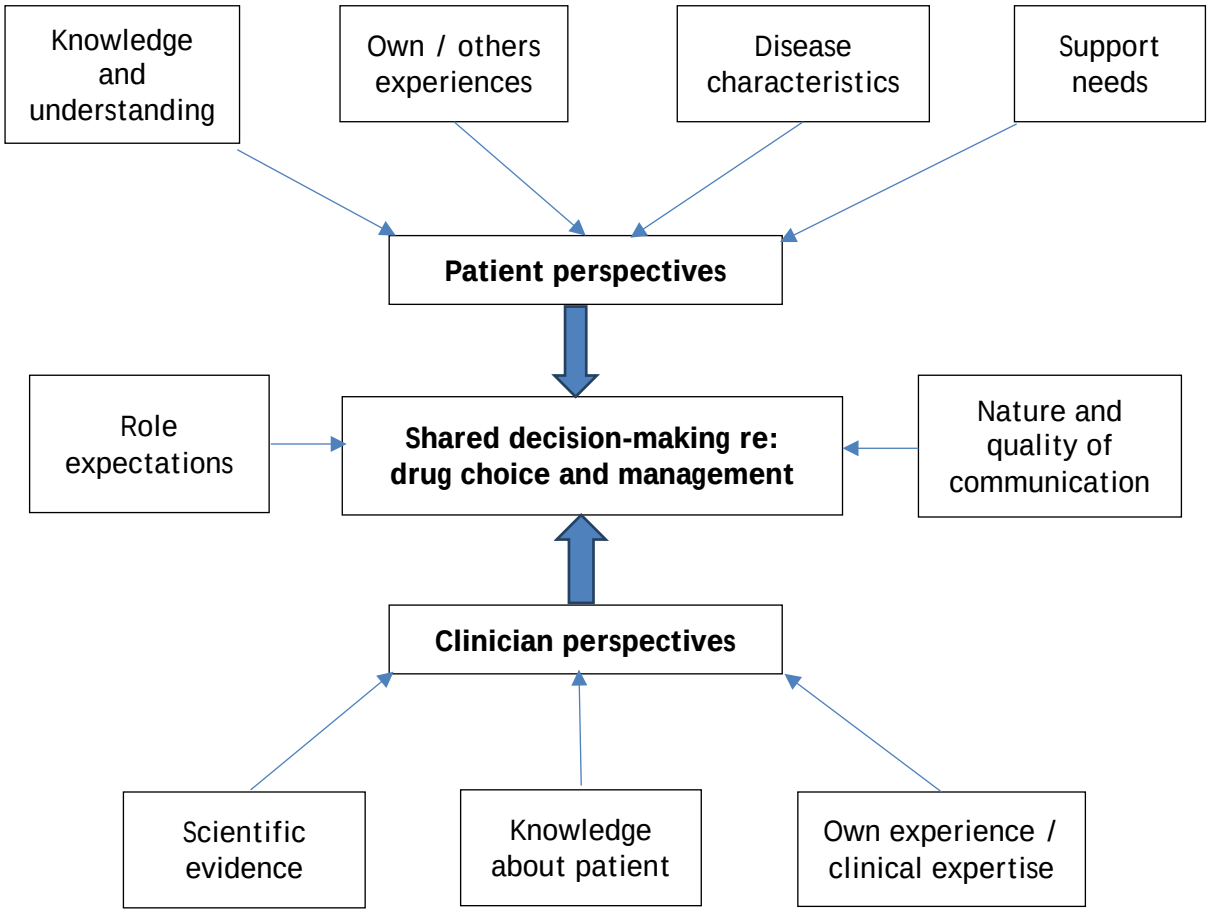
Entezari-Maleki et al. (2016) sought to compare two anticoagulant management services (AMS): pharmacist–managed warfarin therapy (PMWT) versus usual care medicine (UCM) in order to see which would assist patients in managing serious adverse events, such as bleeding and thromboembolic events, but also rates of hospitalisation, visits to emergency departments, cost, patient satisfaction and quality of life. RCTs and non-RCTS were examined to compare PMWT and UCM. This review focused on the findings on patient satisfaction and quality of life. There were 24 studies (of which six reported relevant findings) examining 11,607 participants. Quality assessment of this review was relatively high: 9 of 11 quality criteria were achieved. Patient satisfaction was high: 96% of 221 patients 'very satisfied' or 'satisfied' with the PMWT service compared with 84% of patients in family physician group (p=0.001). Scores for overall satisfaction from treatment and positive emotional affect were significantly higher in PMWT than UMC. The review authors supported PMWT regarding cost saving and patient satisfaction. "The results showed that the PMWT model is superior to UMC in managing warfarin therapy based on observational studies. As well, it is comparable to UMC based on RCT studies." (p24).

Similarly, **Zhou et al. (2016)** also aimed to compare the effectiveness of pharmacist–managed anticoagulant control of warfarin with other models (physicians, nurses, self - managed care) and to tackle the rates of hospitalisation and emergency visits following an adverse event. RCTs were examined both for PMWT and other types of UCM. There were a total of eight studies with 1,493 participants. Quality assessment of this review was high: 10 of 11 quality criteria were achieved. Meta-analysis of the RCTs showed that a statistically significant difference existed between pharmacist-managed care and other models for satisfaction (MD 0.41, 95% CI 0.01 to 0.81; p=0.04, low-quality evidence), with significant heterogeneity. The review authors suggested that pharmacist-managed warfarin anticoagulation therapy; "achieved better anticoagulation control measured as percentage of time within the standard therapeutic range; however, it has similar percentages in the expanded therapeutic range." (p.606). Similarly to Entezari-Maleki et al. (2016), the review authors reported that overall, participants were significantly more satisfied with pharmacist-managed interventions compared with usual care (0.41 (95% CI 0.01 to 0.81; p=0.04), with heterogeneity (p=0.0001, I^2=89%).

Themes across reviews

Taking the findings of these reviews together, several themes emerged. These are illustrated below in **Figure 1**.

Figure 1. Thematic factors influencing OACs utilisation and uptake



Reviews of stakeholders' perspectives of uptake and utilisation broadly focused on two main issues: deciding on an OAC therapy (i.e. choosing warfarin over no therapy, deciding on warfarin v. NOAC) and ongoing anticoagulation management. The reviews suggested a range of factors that that influence patients and clinicians when considering whether to initiate or maintain OAC treatment. Further, both patients and clinicians identified several issues within the clinical encounter itself, which could influence the nature and quality of decisions about initiating OACs and ongoing management.

Patient perspectives

Review authors reported a range of patient factors that could influence their choice of and/or adherence to OACs therapy. These reflected aspects of the patient's knowledge and understanding, their own or others' experiences, their support needs, and characteristics related to the disease condition itself.

Patients' need for knowledge and understanding

Reviews of patients' preferences and values suggested that when considering or continuing OAC therapy, patients appear to highly value stroke prevention. In one review, authors suggested that across included studies and all therapy options, patients valued the efficacy of stroke prevention over any other attribute, including the risk of bleeding (Loewen et al. 2017). Both reviews stated that bleeding risks were important to, or highly valued by patients (Loewen et al. 2017, Wilke et al. 2017). However, one of these also noted that patients' valuation of the risk of bleeding was highly variable and suggested that this was likely to be due to a lack of disclosure of the risk of death from bleeding across included studies (Loewen et al. 2017). Review findings suggested that patients would accept several serious bleeding episodes in order to avoid one stroke (Lahaye et al. 2014; Devereaux et al. 2001; Alonso-Coello et al. 2015). However, this high value placed on stroke prevention may be more likely if patients or those they know have previous experience of stroke or have had prior warfarin use (Loewen et al. 2017). Men and women may prefer different attributes of therapy. While most included studies did not find an association, findings from two primary studies suggested that women assigned more disutility to major bleeding, had an increased treatment threshold, and tolerated fewer major bleeds per stroke (Lahaye et al. 2014). However, women were also more likely to value warfarin therapy over no therapy (Man-Son-Hing et al. 2002). Men were more likely to be decisive about therapy and to make all-or-none decisions despite knowing efficacy or bleeding risk (Lahaye et al. 2014). Findings from the other review suggested that while patients were willing to accept a higher risk of bleeding if a certain threshold in stroke risk reduction could be reached, this value varied across included studies (Wilke et al. 2017). Review authors suggested this variation may have been due to the differences in study designs, patient selection and data collection methods within the review.

Patients' preferences may differ from what is recommended by current guidance or by clinicians. Both reviews of preferences suggested that patient preferences and values related to bleeding risk and stroke risk also differed unpredictably from those that underpin guidance and the attributes preferred by physicians, although data from physicians was not provided in the review by Loewen et al. (2017). Wilke et al. (2017) noted that in one study, 61% fewer patients would be willing to accept OAC therapy than is recommended in clinical guidelines (Protheroe et al. 2001).

Costs to patients also appear to influence patients' therapy decisions. The relationship between stroke risk reduction and risk of bleeding was valued in terms of cost in one review Loewen et al. 2017. One study in this review found that patients were willing to pay two times more per month in medication cost for every 1% reduction in stroke risk compared with bleed risk (Shafrin et al. 2016).

The four reviews of patient perceptions echoed this valuing of efficacy and safety, but further highlighted issues in the way patients acquired and used this knowledge. Mas Dalmau et al. (2017) noted that patients reported using this information to balance the benefits of

warfarin therapy against the risks of bleeding, hematomas or other adverse effects, thereby suggesting that complete information is important. However, findings from other reviews suggest that their knowledge and understanding of the safety and efficacy of recommended therapy options could be limited. In one review, authors noted that not all patients may understand the indications for therapy and management: i.e. that the purpose of medication is to prevent stroke and that INR monitoring was intended to help prevent stroke or bleeding (Mas Dalmau et al. 2017). Two reviews reported that a lack of knowledge could influence patients' choice of therapy and their adherence (Mas Dalmau et al. 2017, Pandya and Bajorek 2017). Related to this, patients' understanding about the risk of bleeding and the purpose of warfarin may have influenced their adherence (Pandya and Bajorek 2017).

Patients' own or others' experience

After drug safety and efficacy, other factors were considered related to patients' management of their condition. Reviews of patient perceptions and attitudes identified a range of factors related to patient experience. For example, patients' (or their family members') previous experiences of stroke or bleed were noted to influence how patients balance their risks of stroke versus bleeding when deciding whether to use warfarin or not (Mas Dalmau et al. 2017). In one review patients concerns about the lack of a reversal agent or antidote influenced their likelihood of switching to NOAC use (Alamneh et al. 2016). The need to take some NOAC drugs more frequently (Pandya and Bajorek 2017, Willett and Morrill 2017) as well as the need for frequent dosage adjustments in warfarin therapy (Pandya and Bajorek 2017) were identified as factors influencing patient satisfaction with therapy or willingness to switch. Reviews of patient perceptions and attitudes also identified the frequency of INR monitoring as a factor influencing their decision/adherence (Alamneh et al. 2016, Mas Dalmau et al. 2017, Pandya and Bajorek 2017). However, it could be seen as a both a burden associated with poor adherence in warfarin therapy (Mas Dalmau et al. 2017, Pandya and Bajorek 2017) or as a way to provide security that patients were within range to prevent stroke or bleeds (Alamneh et al. 2016, Mas Dalmau et al. 2017). Costs related to INR monitoring and travelling to clinics were also suggested to influence adherence (Pandya and Bajorek 2017). Other factors influencing patients' day-to-day management included concerns about diet restrictions (Mas Dalmau et al. 2017, Pandya and Bajorek 2017, Willett and Morrill 2017), drug interactions (Mas Dalmau et al. 2017, Pandya and Bajorek 2017), the effects of alcohol on drug therapy (Mas Dalmau et al. 2017, Pandya and Bajorek 2017, Willett and Morrill 2017), and restrictions on physical activity (Mas Dalmau et al. 2017, Pandya and Bajorek 2017). Here, it was suggested that younger patients who were physically active were more likely to be non-adherent in warfarin therapy (Arnsten et al. 1997).

Within the reviews of patient preferences and values, it appeared that, beyond risk of stroke and risk of bleeding, these day-to-day 'convenience' attributes matter to patients. However, there was wide variation in which is more important and to whom. The reviews also examined a range of other 'convenience' attributes, which included dosage, food/drug interactions, ongoing monitoring, bridging therapy and cost. These were generally valued

below risk of bleeding (Loewen et al. 2017, Wilke et al. 2017). With respect to NOACs, one review suggested that patients may prefer once daily administration, without any food or drug interactions and without the need for bridging or frequent controls (Wilke et al. 2017). However, patients in one study included in Loewen et al. (2017) were found to be willing to pay for a NOAC antidote; but preferences for NOACs over warfarin were diminished by even small costs to the patient (Ghijben et al. 2014). Across included studies in both reviews, patients varied widely in the importance they placed on each of these convenience attributes. Review authors offered a variety of reasons for this variation, including: differences in sociodemographic characteristics, study setting (hospital, clinic, GP or specialist), current treatment or previous blood monitoring (Wilke et al. 2017); latent effects, such as cultural or familial attitudes and personal experiences, as well as how the risks were framed to, and individualised for, the patient based on their preferences (Loewen et al. 2017).

Patients' support needs

The reviews noted a range of support needs identified by patients. Within reviews of perceptions/attitudes, spousal or family support was suggested to influence patient adherence to warfarin (Pandya and Bajorek 2017). Review authors also suggested that busy work schedules may also influence adherence to warfarin therapy, as employed patients in one study were found to be more adherent than unemployed patients (Arnsten et al. 1997). Mas Dalmau et al. (2017) also noted that patients reported an expectation of support from their health care providers and wanted opportunities to check back with clinicians to "increase their confidence" in managing therapy (p7) (Mas Dalmau et al. 2017). Two reviews of interventions to evaluate pharmacist-led OACs management noted that patients were more satisfied with this type of support. In these reviews, authors identified four different types of models in managing anticoagulant therapy or anticoagulant management services (AMS): Usual medical care, pharmacist-managed anticoagulant services (PMAS), nurse-managed anticoagulant services and finally patient-directed models. UMC is normally managed by a healthcare provider such as a physician. The major activities of the pharmacist at clinics include visiting patients and assessing their medical conditions, adjusting warfarin dose based on INR results usually using point-of-care testing (finger stick method), patient consultation and education, monitoring of patients regarding anticoagulation-related adverse effects, and checking drug and dietary interactions with warfarin (p24) (Entezari-Maleki et al. 2016).

In both reviews the pharmacist-led anticoagulation services resulted in high/superior levels of satisfaction from patients. Overall, their effectiveness was higher than other models: "patients believed pharmacists were more expert in anticoagulant therapy compared with their physicians" (p34) (Entezari-Maleki et al. 2016). However, this may not translate out to long-term benefits: one review demonstrated a minimal impact on quality of life in patients on oral anticoagulation therapy (Lalonde et al. 2008).

Disease characteristics influencing patient choices and adherence

Some review authors suggested that characteristics of the disease itself may influence patient choices and adherence. For example, patients may have difficulty remembering to take NOACs due to cognitive decline associated with AF (Alamneh et al. 2016, Pandya and Bajorek 2017), although this may be confounded by the older age of patients (Mas Dalmau et al. 2017). It was also suggested that AF patients may have more difficulty understanding risk and benefits than do patients with VTE (Mas Dalmau et al. 2017). Further, the asymptomatic nature of AF may also prevent patients from realising the risks of their condition and the importance of therapy (Mas Dalmau et al. 2017).

Clinician perspectives

In some reviews, clinicians were reported to be influenced by a different set of factors. These were grouped into three broad themes: the weight of scientific evidence, clinicians' knowledge of the patient, and their own experience.

Clinicians' views of scientific evidence

One review examined physicians' attitudes to the use and underuse of warfarin (Mas Dalmau et al. 2017). Review authors noted that physicians needed enough information establishing the clear efficacy and safety of warfarin in order to foster decision-making around treatment. However, review authors reported that this could be challenging where scientific evidence was so rapidly changing. Related to this, physicians were concerned about the lack of a reversal agent or antidote when considering switching their patients onto a NOAC (Alamneh et al. 2016).

Clinicians' knowledge of their patient

Physicians were also reported to rely on their knowledge of their patients when considering OAC therapy. Individual patient risks such as age and cognition were suggested to influence physician decisions on OAC therapy (Mas Dalmau et al. 2017), as was the patient's likely response to therapy recommendations (Mas Dalmau et al. 2017). Physicians in some studies also reported perceptions that their patients were negative about OAC therapy because they were misinformed by friends, family or other non-medical sources (Mas Dalmau et al. 2017).

Clinicians' experiences

Finally, some primary studies in one review suggested that physicians preferred to rely on their own experience of managing AF over research evidence and recommendations (Mas Dalmau et al. 2017). This may have arisen in part because the research evidence was not necessarily applicable to the patients seen in the physician's practice setting (Mas Dalmau et al. 2017). It was also noted in this review that geriatricians tended to focus on patient risks more than benefits when discussing therapy options, particularly where these patients also had other complicating conditions (Mas Dalmau et al. 2017). Further, three included primary studies from one review noted that physicians interpreted bleeding risks as more important and stroke risk as less important than did patients (Devereaux et al. 2001; Levitan et al. 2013; Sudlow et al. 1998).

Decisions around choice of therapy and management

Both clinicians and patients offered similar insights into factors that took place during the clinical encounter. Two factors were suggested as influences on OAC decision-making and ongoing management: role expectations of patients and clinicians; and the nature of information and quality of communications between patients, clinicians and the wider team of health care providers.

Role expectations

In deciding whether to initiate warfarin treatment, or to consider NOAC use, one review described a range of perspectives from patients and physician participants (Mas Dalmau et al. 2017). Here, authors reported that patients varied across studies in the extent to which they saw decision-making as a shared activity (Bajorek et al. 2009), in their opinions about the patients' responsibility for decision-making (Bajorek et al. 2009), or in their views about the physician's responsibility. This latter was based on their confidence in the physicians' ability or objectivity, or an expectation that it was the physician's role (Dantas et al. 2004; Alonso-Coello et al. 2008). This review also reported variation in the extent to which physicians considered shared decision-making as important. While most of the review's included studies reported physicians supporting shared decision-making (Lipman et al. 2004; Anderson et al. 2007; Alonso-Coello et al. 2008), the amount of patient involvement varied depending on the clarity of the evidence (Anderson et al. 2007; Alonso-Coello et al. 2008), and the physician's perception that patients should be responsible for their own management and even self-monitoring (Bajorek et al. 2007; Carlsen et al. 2007; Alonso-Coello et al. 2008).

Nature and quality of information and communication

Reviews of patient and clinician perceptions and attitudes suggested that information was more easily understood and likely to influence adherence if it was tailored to the patient's situation, detailed enough to meet their decision-making needs and was provided in both written and oral formats (Mas Dalmau et al. 2017). The review authors suggested that patients expressed a desire for more specific information on drug indications and dosages when deciding on a treatment therapy (Mas Dalmau et al. 2017). This review also reported that patients were less satisfied when they felt that not enough information was provided, or when clinicians were not aware of the patient's medical history (Mas Dalmau et al. 2017). Similarly, review authors also noted that physicians in included studies reported that the quality of the communication and information provided would influence whether OAC therapy was adopted (Mas Dalmau et al. 2017). In this review, the authors also concluded that physicians also noted challenges in decision-making related to the involvement of different physicians and lack of communication between professionals (Mas Dalmau et al. 2017).

Reviews of educational or behavioural interventions to facilitate OACs uptake and adherence in patients evaluated a range of interventions to communicate risks and help

patients balance the challenges and risks of therapy against its benefits. However, this review suggested limited effects in fostering patient adherence, facilitating decision-making or improving quality of life (Clarkesmith et al. 2017). Here, only a few included studies had comparable groups and data on information and communication. One intervention which compared individually-received education to usual care demonstrated small and positive effects on anxiety and depression in the education group. The review authors concluded: "Patients participating in both educational interventions and self-monitoring interventions (with education) appear to spend more time within the therapeutic INR range, but pooled analyses of the AF data did not significantly favour self-monitoring plus education over usual care. Evidence is limited, as there were few trials with small samples of AF patients." (p27). Interestingly within this same review, when the intervention involved the use of decision aids, participants reported feeling conflicted in making their own specific choices (Man-Son-Hing et al. 1999; McAlister et al. 2005; Thomson et al. 2007; O'Connor 1995). The authors argued that this decision conflict may be connected to patient adherence by drawing on other researchers work: "By increasing patient knowledge and understanding surrounding atrial fibrillation and oral anticoagulant therapy we may reduce the prevalence of intentional and unintentional non-adherence, and increase patient motivation to adhere, in addition to providing patients with the tools to improve their planning and capability to incorporate the regimen required with vitamin K antagonist therapy into their lifestyle" (Jackson et al. 2014).

Therefore, the patients' intentional or unintentional attitudes towards therapy can play an integral role in uptake behaviour. Review authors suggested that this could be influenced by the beliefs, age and level of knowledge of the patient. For example, an older patient may be at a cognitive disadvantage and demonstrate unintentional poor adherence due to memory loss or poor knowledge and understanding of drug actions and effects in comparison to a younger patient (Clifford et al. 2008). The review authors suggested that memory aids, such as (reminders or tablet dosettes) could assist with this.

Summary

In summary, findings from reviews of patient and physician perceptions, preferences and values, and interventions measuring adherence, satisfaction and quality of life outcomes suggested that patients and most clinicians both value efficacy (i.e. prevention of stroke) first, then prioritise safety (i.e. risk of bleed) when deciding to initiate or change OAC therapy, although limited evidence suggests that geriatricians may prioritise bleeding over efficacy. Due to the variability in which aspects of OAC or NOAC therapy are under consideration, review authors suggested that where efficacy and safety are equal, there exists a need for individualised discussions with patients, which should include a tailored framing of all potential risks from both treatment and side-effects. The review authors recommended that these factors should be integrated into decision-making tools, to help structure discussions with patients about therapy and allow both patients and physicians to clarify their preferences and values. However, interventions to address these issues have

shown limited success, which may be influenced by communication styles, a clarification of which factors matter most to each patient, and the extent to which patients and clinicians feel that the decision to adopt or switch OAC therapy is their responsibility.

9 Discussion and Conclusions

Main findings

The findings of Sterne et al. (2017)'s review indicate that for prevention of stroke and systemic embolism in atrial fibrillation populations, NOACs show advantages over warfarin for most efficacy and safety outcomes. Of these, apixaban (5mg bd) offered the best balance between efficacy and safety and had the highest probability of being most cost-effective. These findings support the use of NOACs for the prevention of stroke and systemic embolism in atrial fibrillation patients and suggest that apixaban (5mg bd) is the best option. There is no strong evidence to support the use NOACs for VTE for:

- primary prevention (compared with low-molecular-weight heparin, (LMWH);
- acute treatment (compared with warfarin); and
- secondary prevention (compared with warfarin and aspirin).

However, in terms of safety, apixaban (5mg bd) and rivaroxaban (15mg bd, then 20mg od) may reduce the risk of major and clinically relevant bleeding, compared with warfarin for the acute and secondary prevention of VTE. Note that for primary prevention of VTE, conclusions should be limited to hip and knee surgery patients, as no trials among patients who were undergoing neurosurgery, gastroenterological surgery or gynaecological surgery were identified.

For secondary prevention of VTE, aspirin was likely to be the most cost-effective alternative to warfarin. These findings provided no evidence that NOACs should replace the use of:

- LMWH for primary prevention of VTE;
- warfarin for acute treatment of VTE; and
- aspirin for the secondary prevention of VTE.

The NICE 2014 guideline on treatment of atrial fibrillation and VTE recommends using NOACs or a vitamin K antagonist (warfarin) as anticoagulant treatment (NICE 2014). Among these treatments, however, no frontrunner is identified for the management of AF and VTE. Rather, guidance states that individual characteristics and preferences should be taken into consideration when deciding which drug to prescribe. By contrast, low-molecular-weight heparin (LMWH) is the standard treatment for reducing the risk of VTE during hospitalisation (primary prevention) (NICE 2016c).

Among AF populations, Sterne et al. (2017)'s findings indicate that NOACs show advantages over warfarin for most efficacy and safety outcomes. Of these, apixaban (5mg bd) offers the best balance between efficacy and safety and had the highest probability of being most cost-effective. However, there were no direct head-to-head comparisons between different NOAC drugs (as all were indirect comparisons from the networks). Sterne et al. (2017) note

that a new trial that directly compares the most promising NOACs and NOAC doses would be prohibitively expensive (if it was to account for a large number of variables including costs, the effect of past events on future hazard ratios, and probabilities of treatment switching) and, therefore, they called for calculations to assess the cost benefit of any potential new trial.

Sterne and colleagues noted that whilst NOACS are easier to take and manage, compared with warfarin (which requires regular monitoring), the efficacy and safety profiles of NOACs may be improved by monitoring and dose adjustment. Evidence on long-term adherence rates of NOACS and the impact of therapeutic monitoring on the safety and efficacy of NOACs, in patients receiving NOACs for AF, may further clarify the role of NOACs in AF populations. Finally, Sterne and colleagues noted that decision making may also be influenced by the current unavailability of an antidote to anticoagulation with NOACs, which are still in the developmental phase, and whilst NOACs are currently more expensive, the cost of these will probably be greatly reduced once generic NOACs become available.

Whilst Sterne and colleagues were careful to keep analyses of the different doses or frequencies of administration (i.e. od or bd) of oral anticoagulants separate and to focus on longest period of follow-up the duration of treatment varied widely across trials. A need for studies with longer follow-up (e.g., data from registries or health records), which would provide evidence on the longer-term safety and cost-effectiveness of NOACs among AF populations (currently mainly based on short-term trial evidence) was therefore identified. They stated that NHS health record data could provide data on absolute event rates, for efficacy and safety outcomes, rather than relative effects (as assessed in their reviews) which would facilitate more reliable estimations of the cost-effectiveness of NOACs for anticoagulation. Overall, Sterne and colleagues concluded that whilst some evidence suggests that NOACs are more effective than warfarin among AF populations, it is unlikely that NOACs will be suitable for all patients with this condition. They noted the importance of identifying which patient cohorts would be better suited to alternative options.

More generally, Sterne and colleagues highlighted that the characteristics of patients in trials may not be generalisable to those in clinical practice, who may be older and have more comorbidities. For example, they noted that it is possible that bleeding complications are higher among patients treated with warfarin in practice, than those in trials, due to more comorbidities and less management of anticoagulation. However, they highlighted additionally that the efficacy of NOACs over warfarin could also be exaggerated due to suboptimal management of INR among patients in the warfarin trial arms. For example, variation in TTR was substantial among the studies on stroke prevention in AF (from 45.1% to 83%). However, due to the low event rates and insufficient replication of intervention comparisons (especially in the reviews on the primary and secondary prevention of VTE), analyses were based on Bayesian fixed-effect models, meaning that investigation of potential moderators (such as mean TTR) of effects was not possible. Finally, it was noted that nearly all trials on NOACs included in the Sterne et al. (2017) reviews were funded by

pharmaceutical companies. In light of these concerns regarding the relevance of the data to clinical populations, we concur with Sterne and colleagues' conclusions that prescribers and patients may like to exercise caution when considering the results of these reviews.

Genotyping may provide a way to tailor drug therapy more effectively for specific populations; however, the located reviews of genotyping did not provide evidence specific to AF and VTE populations. This rendered their findings ungeneralisable to the overview research questions. These reviews were determined to be of low quality and contained considerable overlap of primary studies. The reviews examined four main genotypes: the CYP4F2, the VKORC1, the CYP2C9 and the Apolipoprotein E (ApoE), focused in Asian, Caucasian, African American and Hispanic populations. A very recent review of evidence, published in March 2018, was located too late for inclusion in this overview (King et al. 2018). It examines the clinical utility and cost-effectiveness of genotyping to inform OAC dosing, similarly noting that conclusions are limited by the low quality of the primary studies.

Interventions that focus on improving patient adherence report largely mixed results. Amongst AF patients, limited evidence, of low quality, supports the beneficial effects of education and education plus patient decision aid on TTR. Self-testing interventions showed little evidence of improvements in TTR, and uncertain improvements in self-monitoring care, compared with usual care. Among mixed-diagnoses groups, the low-to-moderate quality evidence suggested that self-testing interventions may improve the INR values in therapeutic range, compared with usual care. However, when examining TTR outcomes, moderate-quality evidence suggested both positive (longer) and negative (shorter) time in therapeutic range for the self-testing intervention, compared with usual care. The evidence for self-management interventions was mixed for both INR and TTR outcomes, with both higher and lower INR numbers in therapeutic range, and shorter and longer time in therapeutic range, compared with usual care. Low-quality meta-analytic evidence indicated that self-management may be as effective as usual care, but does not offer enhancements over and above usual care, in terms of TTR. The variation in findings suggests the presence of potential moderators. However, the evidence for pharmacist-managed anticoagulation (from mixed-quality studies, rated as high and uncertain) was more consistent across the reviews. This suggests that pharmacist-managed anticoagulation may improve TTR, compared with usual care, among mixed-diagnoses groups. There were no reviews evaluating pharmacist-managed anticoagulation services exclusively in populations with AF and none of the interventions were exclusively examined in populations with VTE.

Reviews of stakeholder experiences suggest that patients and most clinicians both value efficacy (i.e. prevention of stroke) first, then prioritise safety (i.e. risk of bleed) when deciding to initiate or change OAC therapy, although limited evidence suggests that some geriatricians may prioritise bleeding over efficacy. Where efficacy and safety of specific therapies have been established, the next priority should be to consider which factors matter to patients and clinicians, and where their preferences lie with respect to decision-

making. This will help guide the balance of supporting patients to decide on a therapy with the clear provision of information and communication of risks, benefits and preferences. Beyond efficacy and safety, patients and clinicians are influenced by a variety of other factors. These include knowledge, experience, changes in patient cognition and memory due to the condition itself, or patient characteristics, such as age, gender, lifestyle, employment status, support needs, or patient-clinician factors, such as communication and perceptions about who bears the responsibility for decision-making. These findings echo those of previous evidence syntheses concerning stakeholder experiences and models of adherence in OAC therapy (Borg et al. 2012; Brown et al. 2012).

Careful elicitation should take place to determine which factors matter to, or could influence patients, before a decision can occur about initiating, continuing or switching OACs (Di Minno et al. 2014). However, our findings from reviews of interventions suggest limited impact from interventions that employ education and/or decision-aids that should identify these needs in order to improve patient knowledge or decision-making. It may be that a lack of recognition of these factors, and the need to assess each patient individually may explain that lack of large improvements in self-monitoring, self-management or educational or decision-making interventions. It may also be that variations in the factors that influence shared decision-making, such as time constraints, provider motivation, decreased continuity of care, preparation for and processes of shared decision-making could also influence the effectiveness of educational and decision-aid interventions in OAC therapy (Legare et al. 2008; Joseph-Williams et al. 2014).

Overview findings also suggest that there is wide variation in patients' and clinicians' attitudes to shared decision-making. This suggests a need to assess both clinicians and patients' attitudes to shared decision-making. By tailoring the decision-making encounter to reflect these values, it may become more likely that patients will both make the decision that they are most satisfied with and will improve their therapy adherence. It may also be that patients' and clinicians' readiness to make a decision changes over time: this should also be studied to determine its impact on OACs decision-making at the point of initiation, continuation and switching OAC therapy.

Finally, patients' identified need for ongoing support could be met through pharmacist-led management interventions, as these suggest patients are more satisfied with pharmacist-managed care, compared with usual care. The integration of community pharmacists into primary care has been recently recommended (Murray 2016).

Quality of reviews and included primary studies

The quality of the included reviews may have influenced the results seen in this overview. While the reviews of efficacy and safety were of high quality, publication bias was not explored; further searches were conducted 2.5 years before publication, no reporting of protocol revisions was provided, and it was unclear whether the risk of bias rating of primary

studies was integrated into the reviews' syntheses. These factors may have served to overestimate the size of meta-analytic effects. The reviews of self-monitoring, genotyping and stakeholder experience were of moderate-to-high quality, but their included primary studies were low-to-moderate quality. This introduces the possibility that review findings could have been influenced by bias operating in primary studies, which could overestimate the size of the reported effects. This should also be taken into consideration when interpreting these reviews' findings.

Overlap of primary studies across reviews

The overlap of primary studies across reviews varied for each synthesis provided here. No primary studies overlapped in the reviews of efficacy and safety, suggesting that findings were not 'double-counted'. Considerable overlap was found in primary studies included across reviews of genotyping. Although only 27% of included primary studies overlapped across reviews, over half of these were found in three or more reviews. Moderate overlap was noted in reviews of self-monitoring (40%) and reviews of stakeholder perspectives (39%); although in both of these primary studies occurred in only two reviews.

It is uncertain whether the overlap of primary studies across qualitative evidence syntheses, such as the review of stakeholder experiences, should be as concerning as for the other syntheses of reviews in this report. The aims of reviews included in the synthesis of stakeholder experiences are quite broad, reflecting the complex nature of drug utilisation and uptake. It has been recommended that where overlap exists, overview authors may select the highest quality most representative review from which to extract findings (Caird et al. 2015; Lunny et al. 2016). Thus efforts to select only one systematic review per topic would likely miss others with important concepts that could add value to the overview (Ballard and Montgomery 2017, McKenzie and Brennan 2017). While it might be suggested that the moderately high overlap of included primary studies could influence the broad conclusions of this overview, it may also be argued that the overlapping nature of the reviews themselves "represent appropriate replications of data analysis by different groups with different viewpoints" (pII-40) (Grimshaw et al. 2002). The issue of overlap in overviews of reviews remains debatable, and guidance on dealing with it is limited (Ballard and Montgomery 2017). Here, we have endeavoured to report the overlap with the review of stakeholder experiences and the other reviews as transparently as possible. However, we were unable to analyse its impact further due to the rapid nature of this project.

Answering overview research questions

This overview of reviews sought to address several inter-related policy questions:

1. What evidence syntheses have been conducted to address the efficacy of UK-approved oral anticoagulant therapy with respect to:
    a. Warfarin versus NOACs in different patient cohorts?
    b. The impact of warfarin versus NOACs on INR clinic capacity?

   c. The evidence for an optimised pathway on self-monitoring?
   d. The evidence for an optimised pathway on genotyping?

2. What evidence syntheses have been conducted to address the safety of UK-approved oral anticoagulant therapy with respect to:

   a. Renal function and the long-term use of NOACs?
   b. Complications associated with warfarin and NOACs including bleeding and stroke risk?

We identified over 400 systematic reviews published within the past four years to address questions of efficacy and safety. To address this question in the available timelines, we chose the most recent, comprehensive well-conducted review (Sterne et al. 2017). This review suggested that among AF populations, NOACs show advantages over warfarin for most efficacy and safety outcomes. Of these, apixaban (5mg bd) offers the best balance between efficacy and safety and had the highest probability of being most cost-effective. There was no strong evidence to support the use of NOACs for VTE for primary prevention (compared with low-molecular-weight heparin (LMWH), acute treatment (compared with warfarin) and secondary prevention (compared with warfarin and aspirin). However, in terms of safety, apixaban (5mg bd) and rivaroxaban (15mg bd, then 20mg od) may reduce the risk of major and clinically relevant bleeding, compared with warfarin, for the acute treatment of VTE. For secondary prevention of VTE, aspirin was likely to be the most cost-effective alternative to warfarin. This review did not report clearly differences in effect by age, gender or ethnicity; nor did it examine INR clinic capacity, different patient cohorts or long-term renal function. Further examination of the remaining recent systematic reviews of efficacy and safety may elicit further information about differential effectiveness. Reviews of genotyping do not yet provide robust evidence specific to AF and/or VTE populations, suggesting an optimised pathway is not yet available. Reviews of interventions to promote self-monitoring, self-management, education and decision-aid use are similarly based on mixed- or low-quality evidence and show small effects, suggesting that more rigorous evaluation is required.

3. What are patient and clinician experiences of UK-approved oral anticoagulant therapy concerning:

   a. The impact of NOACs and warfarin on patient lifestyle?
   b. Medicines adherence and compliance of NOACs and warfarin?
   c. Clinician perceptions of NOACs and warfarin?
   d. Monitoring INRs in patients receiving VKAs and effects on patient adherence?

Findings from reviews of stakeholder experiences suggest that the impact of NOACs and/or warfarin on patient lifestyle and medicines adherence are likely to be affected by a wide range of factors that will be unique to each patient's circumstances. Efficacy and safety of drugs appear to be most highly valued; but a range of other factors could influence decision-

making and adherence. These include patient and clinician knowledge and experience, changes due to the condition itself or to the patient's age or gender, lifestyle or employment status, patient support needs, communication, and perceptions about who bears the responsibility for decision-making. However patient satisfaction, quality of life and decision conflict outcomes in educational and decision-aid interventions are reported as having limited impact; while reviews of pharmacist-led management interventions suggest patients are more satisfied with this care, compared with usual care.

Strengths and limitations

This represents the most current evidence derived from systematic reviews of OAC research and it demonstrates the extent of research synthesis in this area. As an overview, it conforms to systematic review principles (please see the PRISMA checklist in **Appendix 29** for more detail).

However, some limitations should be considered. The overview relies mainly on review-level findings and has a wide focus, which means that some of the detail usually found in a highly focused systematic review, addressing a specific question, is missing. The focus on one comprehensive review of efficacy and safety of OACs may mean that evidence specific to particular patient populations was excluded. Given the large number of systematic reviews identified, and the short project timeline, it was not possible to assess all the available evidence. The decision to limit our examination of efficacy and safety to just one systematic review was pragmatic, for three reasons. First, the policy need for this project meant that a short timeline was necessary, which precluded the amount of time available for locating, assessing and analysing reviews. Second, each of the reviews would have considerable overlap of included primary studies, which would require consideration in analysis and require further time to clarify the true weight of evidence each primary study contributed to each review. Third, the location of a comprehensive, robust, recent and NHS-focused report directly answering our overview research question suggested that there would be little gain in identifying and analysing less relevant reviews.

Conclusions and recommendations for future research

Some questions could not be addressed, or only limited or mixed evidence was identified. New evidence syntheses could usefully address:

- the impact of OACs on renal functions;
- the efficacy of self-monitoring or self-management for a range of conditions in which VTE is a risk factor;
- differences between genotypes in examining clinical outcomes, treatment maintenance and adverse effects specific to AF and VTE populations; and
- the influence of gender and age on the OACs' efficacy, safety, and patient experience.

Research gaps were also apparent and new primary research could address:

- the relationships between age, cognition and memory in AF and VTE populations;
- AF and VTE patients' support needs and preferences with respect to the specific drug therapies recommended by Sterne et al. (2017);
- the most effective strategies to help clinicians assess AF and VTE patients' willingness and ability to decide on OACs therapy;
- self-monitoring and self-management in AF and VTE;
- the limited effectiveness seen in interventions using decision aids; and
- the need for a practical tool to guide clinicians in appraising patients' and their own perception of their role and responsibility when decisions must be made regarding the initiation and maintenance of OACs therapy.

Focusing future research efforts in these areas may help clinicians to understand their choices in prescribing, as well as to better inform patients about treatment options so they can contribute to decisions about OAC therapy. These efforts to improve communication quality may further foster the patient experience in care (Doyle et al. 2013).

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11 Appendices

Appendix 1: Search Strategy terms

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1 Anticoagulants/ (70885)
2 Administration, Oral/ (140536)
3 1 and 2 (5342)
4 (oral$ adj3 anticoagulant$).mp. (11057)
5 (oral$ adj3 anticoagulation).mp. (4884)
6 (OAC adj3 (treat$ or therap$)).ti,ab. (506)
7 DOAC$.mp. (818)
8 NOAC$.mp. (1588)
9 (warfarin or coumadin).ti,ab. (23229)
10 warfarin/ (18867)
11 (apixaban or eliquis).ti,ab. (2180)
12 Dabigatran/ (2503)
13 (dabigatran or pradaxa).ti,ab. (3813)
14 (edoxaban or lixiana).ti,ab. (894)
15 Rivaroxaban/ (2172)
16 (rivaroxaban or xarelto).ti,ab. (3482)
17 Aspirin/ (45105)
18 aspirin.ti,ab. (46772)
19 17 or 18 (65844)
20 Stroke/ or Ischaemic Attack, Transient/ (87442)
21 Myocardial Infarction/ or Venous Thrombosis/ (193741)
22 Thromboembolism/ or Pulmonary Embolism/ or Atrial Fibrillation/ (107659)
23 Anticoagulants/ (70885)
24 20 or 21 or 22 or 23 (410719)
25 19 and 24 (12727)
26 (aspirin adj3 (stroke$ or transient ischaemic attack$ or transient ischemic attack$ or TIA or heart attack$)).ti,ab. (822)
27 (aspirin adj3 (thrombosis or embolism or thromboembolism or atrial fibrillation)).ti,ab. (337)
28 (aspirin adj3 anticoagul$).ti,ab. (689)
29 "Vitamin K"/ (11631)
30 vitamin K.ti,ab. (13391)
31 29 or 30 (19806)
32 31 and 24 (5825)
33 (vitamin K adj3 (stroke$ or transient ischaemic attack$ or transient ischemic attack$ or TIA or heart attack$)).ti,ab. (67)

34 (VKA$ adj3 (stroke$ or transient ischaemic attack$ or transient ischemic attack$ or TIA or heart attack$)).ti,ab. (62)
35 (vitamin K adj3 (thrombosis or embolism or atrial fibrillation)).ti,ab. (125)
36 (VKA$ adj3 (thrombosis or embolism or thromboembolism or atrial fibrillation)).ti,ab. (67)
37 (vitamin K adj3 anticoagul$).ti,ab. (1549)
38 vitamin K antagonist$.ti,ab. (4736)
39 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 25 or 26 or 27 or 28 or 32 or 33 or 34 or 35 or 37 or 38 (54568)
40 Meta-Analysis as Topic/ (17376)
41 meta analy$.tw. (132487)
42 metaanaly$.tw. (1966)
43 Meta-Analysis/ (94843)
44 (systematic adj (review$1 or overview$1)).tw. (121548)
45 exp Review Literature as Topic/ (10322)
46 or/40-45 (237989)
47 cochrane.ab. (61716)
48 embase.ab. (65920)
49 (psychlit or psyclit).ab. (957)
50 (psychinfo or psycinfo).ab. (22044)
51 (cinahl or cinhal).ab. (20870)
52 science citation index.ab. (2933)
53 cancerlit.ab. (679)
54 or/47-53 (106215)
55 reference list$.ab. (15901)
56 bibliograph$.ab. (16317)
57 hand-search$.ab. (6091)
58 relevant journals.ab. (1104)
59 manual search$.ab. (3840)
60 55 or 56 or 57 or 58 or 59 (38732)
61 selection criteria.ab. (28310)
62 data extraction.ab. (16717)
63 61 or 62 (42844)
64 Review/ (2480860)
65 63 and 64 (28687)
66 comment/ (735999)
67 letter/ (1035172)
68 editorial/ (470242)
69 animal/ (6598857)
70 human/ (18058112)
71 69 not (69 and 70) (4708497)
72 66 or 67 or 68 or 71 (6336983)
73 46 or 54 or 60 or 65 (284883)
74 73 not 72 (270201)
75 39 and 74 (2082)

76 qualitative systematic review$.ti,ab. (511)
77 (systematic review and qualitative).ti,ab. (5075)
78 evidence synthesis.ti,ab. (3012)
79 realist synthesis.ti,ab. (155)
80 (qualitative and synthesis).ti,ab. (5761)
81 (meta-synthesis$ or meta synthesis$ or metasynthesis$).ti,ab. (868)
82 (meta-ethnograph$ or metaethnograph$ or meta ethnograph$).ti,ab. (412)
83 (meta-study or metastudy or meta study).ti,ab. (85)
84 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 (12431)
85 39 and 84 (23)
86 75 or 85 (2088)
87 limit 86 to yr="2014 -Current" (895)

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Appendix 2: AMSTAR Quality appraisal

1. Did the research questions and inclusion criteria for the review include the components of PICO? Yes/No

For Yes:	Optional (recommended)
Population	Timeframe for follow-up
Intervention	
Comparator group	
Outcome	

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? Yes/Partial Yes/No

For Partial Yes:	For Yes:
The authors state that they had a written protocol or guide that included ALL the following:	As for partial yes, plus the protocol should be registered and should also have specified:
• review question(s) • a search strategy • inclusion/exclusion criteria • a risk of bias assessment	• a meta-analysis/synthesis plan, if appropriate, *and* • a plan for investigating causes of heterogeneity • justification for any deviations from the protocol

3. Did the review authors explain their selection of the study designs for inclusion in the review? Yes/No

For Yes, the review should satisfy ONE of the following:
- Explanation for including only RCTs
- OR Explanation for including only NRSI
- OR Explanation for including both RCTs and NRSI

4. Did the review authors use a comprehensive literature search strategy? Yes/Partial Yes/No

For Partial Yes (all the following):	For Yes, should also have (all the following):

• searched at least 2 databases (relevant to research question) • provided key word and/or search strategy • justified publication restrictions (e.g. language)	• searched the reference lists / bibliographies of included studies • searched trial/study registries • included/consulted content experts in the field • where relevant, searched for grey literature • conducted search within 24 months of completion of the review

5. Did the review authors perform study selection in duplicate? Yes/No

For Yes, either ONE of the following:
- at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

6. Did the review authors perform data extraction in duplicate? Yes/No

For Yes, either ONE of the following:
- at least two reviewers achieved consensus on which data to extract from included studies
- OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

7. Did the review authors provide a list of excluded studies and justify the exclusions? Yes/Partial Yes/No

For Partial Yes:	For Yes must also have:
provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	justified the exclusion from the review of each potentially relevant study

8. Did the review authors describe the included studies in adequate detail? Yes/Partial Yes/No

For Partial Yes (ALL the following):	For Yes should also have ALL the following:

• described populations • described interventions • described comparators • described outcomes • described research designs	• described population in detail • described intervention in detail (including doses where relevant) • described comparator in detail (including doses where relevant) • described study's setting • timeframe for follow-up

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?

RCTs		
For Partial Yes, must have assessed RoB from:	For Yes, must also have assessed RoB from:	Yes Partial Yes No Includes only NRSI
• unconcealed allocation, and • lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	• allocation sequence that was not truly random, and • selection of the reported result from among multiple measurements or analyses of a specified outcome	
NRSI		
For Partial Yes, must have assessed RoB:	For Yes, must also have assessed RoB:	Yes Partial Yes No Includes only RCTs
• from confounding, and • from selection bias	• methods used to ascertain exposures and outcomes, and • selection of the reported result from among multiple measurements or analyses of a specified outcome	

10. Did the review authors report on the sources of funding for the studies included in the review? Yes/No

For Yes:
- Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? Yes/No/No meta-analysis conducted

RCTs for Yes:

- The authors justified combining the data in a meta-analysis
- AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
- AND investigated the causes of any heterogeneity

NRSI for Yes:

- The authors justified combining the data in a meta-analysis
- AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
- AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
- AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

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? Yes/No/No meta-analysis conducted

For Yes:

- included only low risk of bias RCTs
- OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? Yes/No

For Yes:

- included only low risk of bias RCTs
- OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? Yes/No

For Yes:

- There was no significant heterogeneity in the results
- OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

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? Yes/No/No meta-analysis conducted

For Yes:

- performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? Yes/No

For Yes:

- The authors reported no competing interests OR
- The authors described their funding sources and how they managed potential conflicts of interest.

Appendix 3: JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses

Reviewer _____Date _____

Author _____Year _____Record Number_____

	Yes	No	Unclear	Not applicable
1. Is the review question clearly and explicitly stated?	☐	☐	☐	☐
2. Were the inclusion criteria appropriate for the review question?	☐	☐	☐	☐
3. Was the search strategy appropriate?	☐	☐	☐	☐
4. Were the sources and resources used to search for studies adequate?	☐	☐	☐	☐
5. Were the criteria for appraising studies appropriate?	☐	☐	☐	☐
6. Was critical appraisal conducted by two or more reviewers independently?	☐	☐	☐	☐
7. Were there methods to minimize errors in data extraction?	☐	☐	☐	☐
8. Were the methods used to combine studies appropriate?	☐	☐	☐	☐
9. Was the likelihood of publication bias assessed?	☐	☐	☐	☐
10. Were recommendations for policy and/or practice supported by the reported data?	☐	☐	☐	☐
11. Were the specific directives for new research appropriate?	☐	☐	☐	☐

Overall appraisal: Include □ Exclude □ Seek further info □
Comments (Including reason for exclusion)

Appendix 4: Flow of literature through the review

Criteria on which reports were excluded (abstract and full text)

Exclude 1: date of publication (pre 2014)

Exclude 2: not reported in the English language

Exclude 3: not an OECD country

Exclude 4: not a systematic review

Exclude 5: Children (aged 17 or younger)

Exclude 6: not focused on anticoagulation

Exclude 7: focus not on UK recommended OACs

Exclude 8: not on stroke prevention in non-valvular AF or prevention/treatment of VTE

Exclude 9: intervention is polypharmacy in nature

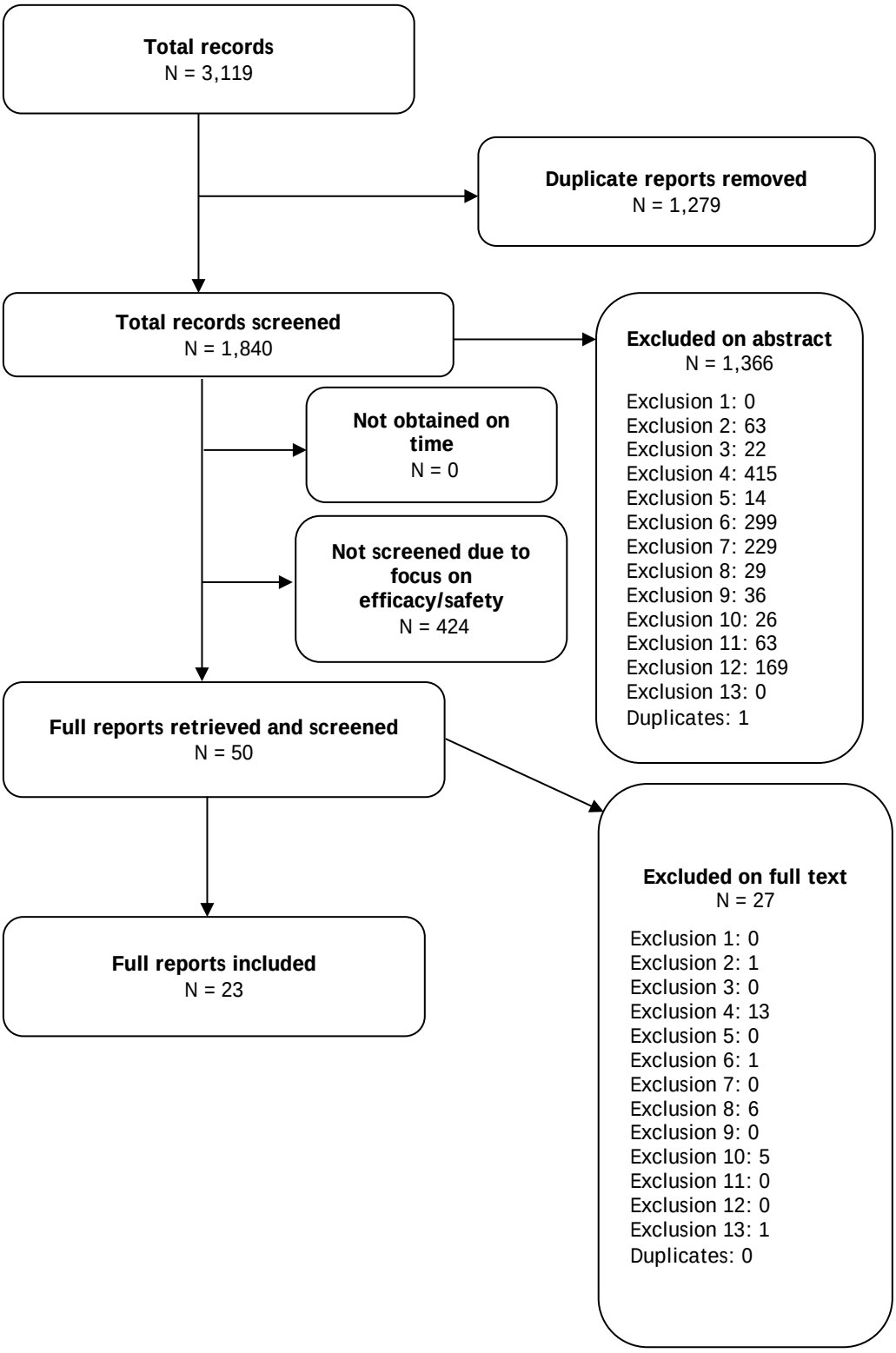
Exclude 10: topic: does not focus on drug efficacy/safety, adherence, experiences

Exclude 11: no comparator (applies to quantitative studies only)

Exclude 12: on comparator type (if drug efficacy/safety)

Exclude 13: does not include health or cost outcomes

Exclude 14: duplicate



Appendix 5: Reference list of economic reviews

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Appendix 7: Effectiveness, safety and cost-effectiveness review; UK-licensed doses of the NOACs

NOAC	AF	VTE treatment	VTE primary prevention	VTE secondary prevention
Rivaroxaban	20mg od	15mg/20mg bd	10mg od	15mg/20mg od[74]
Edoxaban	60mg od	60mg od[75]		60mg od[76]
Dabigatran	150mg bd	150mg bd	220mg od	150mg bd
Apixaban	5mg bd	10mg/5mg bd	2.5mg bd	2.5mg bd[77]
Betrixaban[78]				

Source: https://cks.nice.org.uk/anticoagulation-oral#!management

[74] Only 20mg in the analyses
[75] Or 30mg od (17.6%) in the analyses
[76] Not included in analyses
[77] Also 5mg in the analyses
[78] 40mg as the licensed dose in the analyses for AF

Appendix 8: Effectiveness, safety and cost-effectiveness review; summary of the reviews

Study Author (year)	Topic Focus	Search + Year range of synthesised studies	Studies included	Included primary studies relevant to ths review
Sterne et al. (2017); Review 1	**Prevention of AF-related stroke:** efficacy, safety & cost-effectiveness	**Search:** Databases searched in March 2014 and updated in September 2014. **Year range of included studies:** 1989 to 2014	**Number reviewed:** 23 (41 articles) **Related to AF/VTE adult population:** 23 (AF) **Type of study:** RCTs	The ACTIVE Writing Group 2006; Petersen et al. 1989; Gulløv et al. 1998; Liu et al. 2014; Yamaguchi 2010; Chung et al. 2011; Garcia et al. 2010; Weitz et al. 2010; Chen et al. 2012; Lopes et al. 2010; Granger et al. 2011; Hohnloser et al. 2012; Easton et al. 2012; Flaker et al. 2013; Al-Khatib et al. 2013; Bahit et al. 2013; Garcia et al. 2013; McMurray et al. 2013; Alexander et al. 2014; Hylek et al. 2014; Ogawa et al. 2011; Eikelboom et al. 2010; Hohnloser et al. 2011; Connolly et al. 2011; Diener et al. 2012; Mant et al. 2007; Hu et al. 2006; Ruff et al. 2010; Giugliano et al. 2013; Connolly et al. 2013; Hori et al. 2012; Hellemons et al. 1999; Ezekowitz et al. 2007; Connolly et al. 2009; Connolly et al. 2010; ROCKET AF Study Investigators 2010; Patel et al. 2011; Hankey et al. 2012; Mahaffey et al. 2013; Stroke Prevention in Atrial Fibrillation Investigators 1994; Rash et al. 2007
Sterne et al. (2017); Review 2	**VTE primary prevention:** efficacy, safety & cost-effectiveness	**Search:** Databases searched in March 2014 and updated in September 2014. **Year range of included studies:** 1996 to 2012	**Number reviewed:** 43 (46 articles) **Related to AF/VTE adult population:** 43 (VTE) **Type of study:** RCTs	Goldhaber et al. 2011; Lassen et al. 2009; Lassen et al. 2010b; Lassen et al. 2010a; Lassen et al. 2007; Heit et al. 1997; Eriksson et al. 2005; Turpie et al. 2009a; Kakkar et al. 2011; Cohen et al. 2010; Cohen et al. 2013; Eriksson et al. 2007a; Eriksson et al. 2006a; Turpie et al. 2005; Eriksson et al. 2006b; Agnelli et al. 2009; Eriksson et al. 2008; Kakkar et al. 2008; Lassen et al. 2008; Turpie et al. 2009b; Ginsberg et al. 2009; Eriksson et al. 2007c; Eriksson et al. 2007b; Eriksson et al. 2010; Eriksson et al. 2011; Fuji et al. 2010d; Fuji et al. 2009a; Fuji et al. 2010b; Fuji et al. 2009b; Fuji et al. 2014, Fujita et al. 2010; Fuji et al. 2010c; Haas et al. 2012; Levine et al. 2012; Iliopoulos et al. 2011; Fuji et al. 2010a; Raskob et al. 2010; Goel et al. 2009; Yokote et al. 2011; Kanan et al. 2008; Zhang et al. 2013; Leclerc et al. 1996; Francis et al. 1997; Colwell et al. 1999; Hull et al. 2000; Fitzgerald et al. 2001

Study Author (year)	**Topic Focus**	**Search + Year range of synthesised studies**	**Studies included**	**Included primary studies relevant to ths review**
Sterne et al. (2017); Review 3	**Acute treatment of VTE**: efficacy, safety & cost-effectiveness	**Search:** March 2014, updated September 2014 **Year range of included studies:** 2007 to 2014	**Number reviewed:** 9 (10 articles) **Related to AF/VTE adult population:** 9 (VTE) **Type of study:** RCTs	Hokusai et al. 2013; Agnelli et al. 2007; Büller et al. 2008; Schulman et al. 2009; Bauersachs et al. 2010**;** Büller et al. 2012; Raskob et al. 2013; Hokusai et al. 2013; Agnelli et al. 2013; Schulman et al 2014
Sterne et al. (2017); Review 4	**Secondary prevention of VTE**: efficacy, safety & cost-effectiveness	**Search**: March 2014, updated September 2014 **Year range of included studies**: 1999 to 2013	**Number reviewed:** 10 (11 articles) **Related to AF/VTE adult population:** 10 (VTE) **Type of study:** RCTs	Agnelli et al. 2012; Brighton et al. 2012; Buller 2009; The EINSTEIN Investigators 2010; Romualdi et al. 2011; Kearon et al. 1999; Ridker et al. 2003; Schulman et al. 2013; Becattini et al. 2012; Agnelli et al. 2001; Agnelli et al. 2003

Appendix 9: Effectiveness, safety and cost-effectiveness review; detailed characteristics of the four reviews

Review	Number of studies reviewed	Sample size	Population character-istics	Number of studies reporting primary outcomes	Anticoagulants directly compared (k)	Targeting population	Setting and follow-ups (k)	Primary outcomes[79] (k)	Quality appraisal tool
Prevention of AF-related stroke	23 (AF)	**Total:** 94,656 **Range:** From 75 to 21,105	**Mean age:** Ranged from 63.3 to 81.5 years NR: 9 **Gender:** Male (%) ranged from 44.9 to 82.9 NR: 5 **Ethnicity:** NR	23	**NOACs vs warfarin (12)** Apixaban (2) Dabigatran (3) Edoxaban (4) Rivaroxaban (2) Betrixaban (1) **Other comparisons (11):** Antiplatelet v warfarin (9) Antiplatelet v apixaban (1) Antiplatelet v antiplatelet and warfarin (1)	**Age:** Adults ≥ 18 years **Health condition:** People with non valvular AF, with or without previous stroke, hypertension or chronic heart failure	**Setting:** Primary care and anticoagulation clinics **Treatment duration (months):** Ranged from 3 to 42; NR: 2. **Mean time in therapeutic range for warfarin (%):** Ranged from 45.1 to 83; NR: 7/21.	**Efficacy:** Stroke or systemic embolism (15); Ischaemic stroke (13); myocardial infarction (15) **Safety:** Major bleeding (18); CRB (12); intracranial bleeding (6); all-cause mortality (18)	Cochrane Risk of Bias Tool

[79] Not mutually exclusive, i.e. the numbers do not add up since most trials assessed more than one intervention and outcome.

Review	Number of studies reviewed	Sample size	Population character-istics	Number of studies reporting primary outcomes	Anticoagulants directly compared (k)	Targeting population	Setting and follow-ups (k)	Primary outcomes[79] (k)	Quality appraisal tool
VTE – Primary prevention	43 (VTE)	**Total:** 77,563 **Range:** From 67 to 8,323	**Mean age:** Ranged from 41 to 76 years NR: 5 **Gender:** Male (%) ranged from 13.1 to 62.7 NR: 5 **Ethnicity:** NR	43[80]	**NOACs v LMWH (27):** Apixaban (4) Dabigatran (6) Edoxaban (5) Rivaroxaban (11) Betrixaban (1) **NOACs v LMWH and warfarin (1):** Apixaban (1) **NOACs v placebo (3):** Apixaban (1) Dabigatran (1) Edoxaban (1) **Other comparisons (12):** LMWH v warfarin (6) LMWH v placebo (6)	**Age:** Adults ≥ 18 years **Health conditions:** Hip surgery (18) Knee surgery (17) Hip & knee surgery (1) Other medical conditions (7)	**Setting:** Hospital **Treatment duration (days):** Ranged from 4 to 182.6[81]; NR: 1 **Mean time in therapeutic range for warfarin (%):** NR in any of the primary studies with warfarin (7/7)	**Efficacy:** Symptomatic VTE (29)[82]; symptomatic DVT (25); symptomatic PE (35) **Safety:** Myocardial infarction (9); major bleeding (39); CRB (27); all-cause mortality (28)	Cochrane Risk of Bias Tool

[80] 38 RCTs were included in the analyses, with the exception of major bleeding (39).
[81] The majority of treatment durations for the primary studies were reported as ranges. The shortest and longest durations for all trials were noted.
[82] 28 trials were included in the analyses for VTE, 20 for DVT, 30 for PE, nine for MI, 34 for major bleeding, 25 for CRB, and 24 for mortality.

Review	Number of studies reviewed	Sample size	Population character-istics	Number of studies reporting primary outcomes	Anticoagulants directly compared (k)	Targeting population	Setting and follow-ups (k)	Primary outcomes[79] (k)	Quality appraisal tool
VTE – Acute treatment	9 trials (VTE; referenced in 10 articles)	**Total:** 28,803 **Range:** From 520 to 8,292	**Mean age:** Ranged from 54.7 to 59.1years NR: 0 **Gender:** Male (%) ranged from 51% to 62% NR: 0 **Ethnicity:** NR	9	**NOACs v warfarin (9):** Apixaban (2) Rivaroxaban (4) Edoxaban (1) Dabigatran (2)	**Age:** Adults ≥ 18 years **Health conditions:** New or recurrent objectively confirmed diagnosis of acute symptomatic VTE	**Setting:** Hospital **Treatment duration** 12 to 48 weeks **Mean time in therapeutic range for warfarin (%):** 56.9 to 63.5	**Efficacy:** Symptomatic VTE (8)[83]; symptomatic DVT (9); symptomatic PE (9); MI (5) **Safety:** Major bleeding (9); CRB (8); all-cause mortality (8)	Cochrane Risk of Bias Tool
VTE – Secondary prevention	10 (VTE)	**Total:** 10,390 **Range:** From 162 to 2,866	**Mean age:** Ranged from 53 to 67.3 years NR: 1 **Gender:** Male (%) ranged from 52.8 to 63.9	10	**NOACs v warfarin (1):** Dabigatran (1) **NOACs v placebo (3):** Apixaban (1) Dabigatran (1) Rivaroxaban (1)	**Age:** Adults ≥ 18 years **Health conditions:** On anticoagulants for 3 months or more after	**Setting:** Primary care and anticoagulation clinics **Treatment duration (months):** Ranged from 3 to 51.6; NR: 0.	**Efficacy:** Symptomatic VTE (10); symptomatic DVT (9); symptomatic PE (9) **Safety:** Myocardial infarction (5); major bleeding	Cochrane Risk of Bias Tool

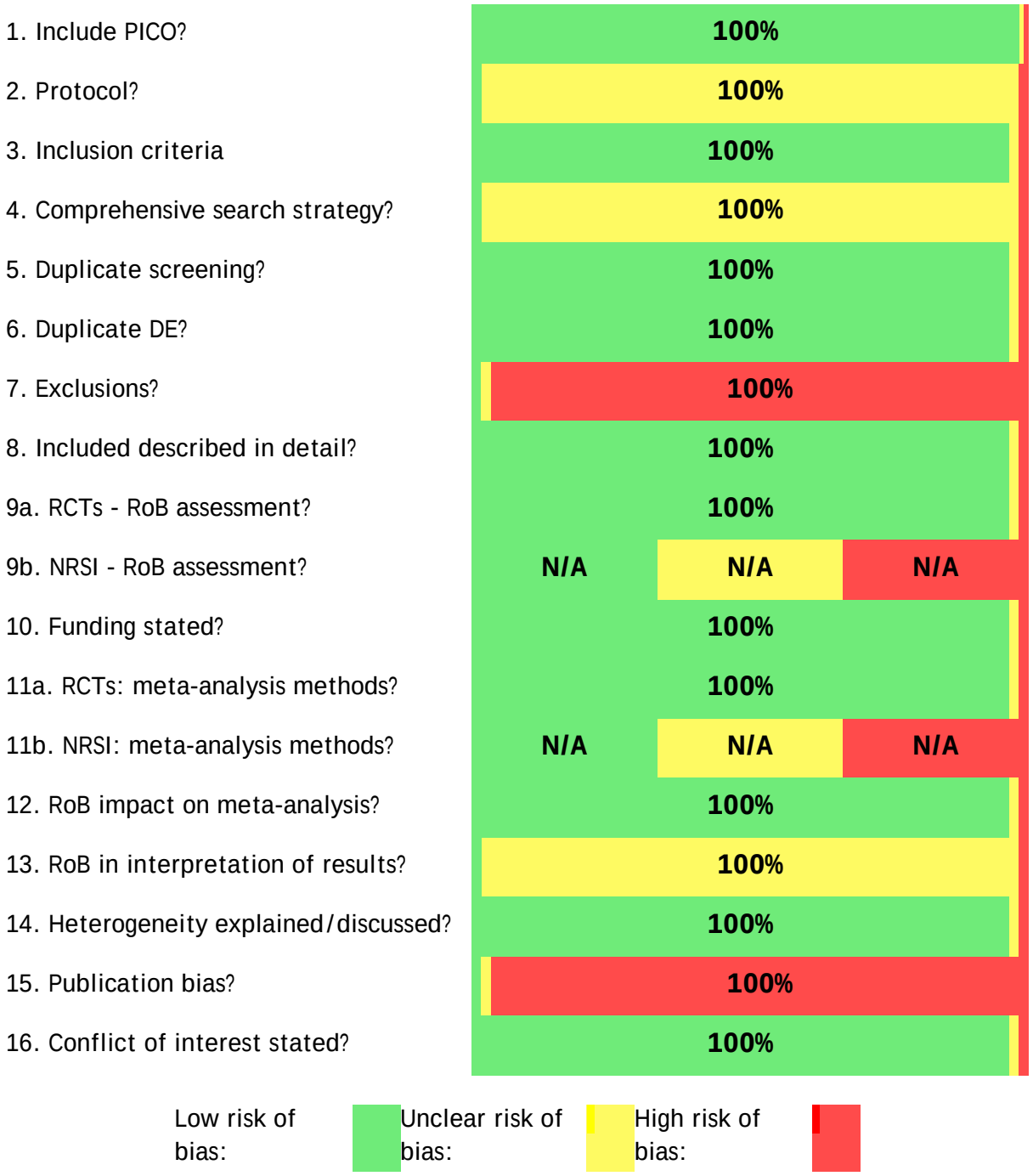
[83] Table 107 in Sterne's report shows eight studies with this outcome, while the summary (p171) only mentions seven.

Review	Number of studies reviewed	Sample size	Population character-istics	Number of studies reporting primary outcomes	Anticoagulants directly compared (k)	Targeting population	Setting and follow-ups (k)	Primary outcomes[79] (k)	Quality appraisal tool
			NR: 0 **Ethnicity:** NR		**Other comparisons (6):** Warfarin v placebo (2) Warfarin v no treatment (2) Aspirin v placebo (2)	a first VTE, without recurrence	NOACs only: 6 to 36; NR: 0 **Mean time in therapeutic range for warfarin (%):** Values: 64 and 81; NR: 3/5. Median with dabigatran: 65.3	(10); CRB (6); all-cause mortality (9)	

Appendix 10: Effectiveness, safety and cost-effectiveness review; risk of bias assessment of included reviews

	1	2	3	4	5	6	7	8	9a	9b	10	11a	11b	12	13	14	15	16
First author (year); Review	Include PICO?	Protocol?	Inclusion criteria	Comprehensive search strategy?	Duplicate screening?	Duplicate DE?	Exclusions?	Included described in detail?	RCTs - RoB assessment?	NRSI - RoB assessment?	Funding stated?	RCTs: Appropriate meta-analysis methods?	NRSI: Appropriate meta-analysis methods?	RoB impact on meta-analysis?	RoB in interpretation of results?	Heterogeneity explanation/discussion?	Publication bias?	Conflict of interest stated?
Sterne (2017); Review 1	+	PY[a]	+	PY[b]	+	+	-	+	+	N/A	+	+	N/A	+	PY[c]	+	-	+
Sterne (2017); Review 2	+	PY[a]	+	PY[b]	+	+	-	+	+	N/A	+	+	N/A	+	PY[c]	+	-	+
Sterne (2017); Review 3	+	PY[a]	+	PY[b]	+	+	-	+	+	N/A	+	+	N/A	+	PY[c]	+	-	+
Sterne (2017); Review 4	+	PY[a]	+	PY[b]	+	+	-	+	+	N/A	+	+	N/A	+	PY[c]	+	-	+

PY = partial yes, N/A = not applicable, a = there was no statement to say whether and to what extent deviations from the protocol were made, b = the search was last updated 2.5 years before publication, c = it is unclear whether the risk of bias was integrated into the data synthesis. The terminology relating to evidence (e.g., little evidence) was not clearly defined.


1. Include PICO?
100%
2. Protocol?
100%
3. Inclusion criteria
100%
4. Comprehensive search strategy?
100%
5. Duplicate screening?
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6. Duplicate DE?
100%
7. Exclusions?
100%
8. Included described in detail?
100%
9a. RCTs - RoB assessment?
100%
9b. NRSI - RoB assessment?
N/A
N/A
N/A
10. Funding stated?
100%
11a. RCTs: meta-analysis methods?
100%
11b. NRSI: meta-analysis methods?
N/A
N/A
N/A
12. RoB impact on meta-analysis?
100%
13. RoB in interpretation of results?
100%
14. Heterogeneity explained/discussed?
100%
15. Publication bias?
100%
16. Conflict of interest stated?
100%
Low risk of bias:
Unclear risk of bias:
High risk of bias:

Appendix 11: Effectiveness, safety and cost-effectiveness review; summary of the relevant main conclusions of the four reviews and the cost-effectiveness analyses

Review	Network meta-analytic comparisons involving Warfarin (INR 2-3) and/or NOACs[84]	Rankogram and cost-effectiveness analyses
Prevention of stroke related to AF (Review 1)	NOACs show advantages over warfarin for all efficacy and safety outcomes with few exceptions: • Edoxaban (30 and 60mg bd) may increase risk of clinically relevant bleeding (CRB) and ischaemic stroke (30mg od) • Dabigatran (110mg and 150mg bd, and edoxaban 30mg od) may increase risk of myocardial infarction	Among the treatments warfarin (INR 2–3); dabigatran (150mg bd); edoxaban (60mg od); rivaroxaban (20mg od); apixaban (5mg bd); antiplatelet therapy (≥ 150mg od): • The non-NOAC interventions (warfarin and antiplatelet therapy; aspirin/clopidogrel >= 150mg bd) were ranked worst for stroke or systemic embolism, and were not among the best three for any outcome • Apixaban (5mg bd) was likely to be one of the best anticoagulants to prevent stroke or systemic embolism, Ischemic stroke, myocardial infarction, major bleeding, intracranial bleeding and all-cause mortality. It also had the highest probability of being most cost-effective
VTE primary prevention (Review 2)	There is no strong evidence to support the use NOACs for the primary prevention of VTE There were no comparisons between warfarin and NOACs	Among the treatments warfarin (INR 2–3); apixaban (2.5mg bd); dabigatran (220mg bd); rivaroxaban (10mg od); LMWH post/pre-op (standard dose)[85]: • Warfarin was likely to be the best for reducing the risk of major bleeding • Low-molecular-weight heparin (LMWH; post-op, standard dose)[85] was the best or second-best for reducing the risk of CRB

[84] Comparisons with a ratio, between the confidence interval limits, that exceeded nine were considered to be imprecise.
[85] Standard dose for LMWH included tinzaparin (0.45mL od), enoxaparin (40mg od or 30mg bd) and dalteparin (5,000 IU).

Review	Network meta-analytic comparisons involving Warfarin (INR 2-3) and/or NOACs[84]	Rankogram and cost-effectiveness analyses
		• Rivaroxaban (10mg od) had higher risk of major and CRB than LMWH (post-op, standard dose)[85] • For both hip and knee, Rivaroxaban was likely to be the most cost-effective up to willingness-to-pay thresholds of approximately £20,000 per QALY (with high uncertainty for hip surgery)
VTE acute treatment (Review 3)	NOACs showed no efficacy advantage over warfarin, but apixaban (5mg bd) and rivaroxaban (15mg bd, then 20mg od) may reduce the risk of major and clinically relevant bleeding than with warfarin	Among the treatments warfarin (INR 2-3), apixaban (5mg bd), dabigatran (150mg od), edoxaban (60mg or 30mg (17.6%)[86] od) and rivaroxaban (15mg bd then 20mg od): • Apixaban (5mg bd) had a high probability of being ranked best for risk of major and clinically relevant bleeding, and of being ranked best, or second best, for symptomatic DVT, symptomatic VTE and all-cause mortality • Warfarin had a high probability of being ranked worst for major bleeding and CRB • Apixaban (5mg bd) is likely to be the most cost-effective alternative to warfarin for a willingness-to-pay threshold of £20,000-30,000 per QALY, although rivaroxaban and dabigatran could be the most cost-effective, even at high thresholds

[86] In the edoxaban trial, 17.6% of participants received the 30mg dose, while the remaining participants received the 60mg dose (twice daily).

Review	Network meta-analytic comparisons involving Warfarin (INR 2-3) and/or NOACs[84]	Rankogram and cost-effectiveness analyses
VTE secondary prevention (Review 4)	No clear evidence of differences between NOACs and warfarin For symptomatic PE, the risk was higher with apixaban (2.5mg bd) than warfarin Risks of clinically relevant bleeding and major bleeding were lower with apixaban (2.5 or 5mg) and dabigatran (150mg) than with warfarin, with lower risk for apixaban than dabigatran	Rankogram analyses could not be performed due to the substantial proportion of imprecise estimates Aspirin was likely to be the most cost-effective alternative to warfarin at willingness-to-pay thresholds of £20,000 and £30,000 per QALY. But it was uncertain whether it was better than no treatment. Furthermore, evidence suggested that NOACs may reduce the risks of VTE and DVT, compared with aspirin

Appendix 12: Effectiveness, safety and cost-effectiveness review; main findings by outcome for the review on the prevention of AF-related stroke (Review 1)

Outcomes	Included in the network: primary studies,[87] interventions,[88] and events	Risk of bias: number of studies/total	Summary of the network meta-analytic findings[89]		
			NOACs vs warfarin (INR 2-3)	NOACs vs NOACs	Comparisons among other interventions
Stroke or systemic embolism	Primary studies: 23 Interventions: 26 Events: 3,217	Low in all six domains: 2/23 High in one or more domains: 14/23 Unclear in one or more domains, none high: 7/23	Evidence that NOACS apixaban (5mg bd), dabigatran (150mg bd), edoxaban (60mg od) and rivaroxaban (20mg od) may have a lower risk than warfarin.	Evidence that risk may be lower with dabigatran (150mg bd) compared with edoxaban (60mg od) and rivaroxaban (20mg od).	*Antiplatelets increased the risk, compared with warfarin.*
Ischaemic stroke	Primary studies: 14 Interventions: 15 Events: 2,228	Low in all six domains: 2/14 High in one or more domains: 7/14 Unclear in one or more domains, none high: 5/14	Evidence that dabigatran (150mg bd) may have a lower risk than warfarin, while edoxaban (30mg od)'s risk may be higher than warfarin.	Little evidence of differences in risk.	*Antiplatelets increased the risk, compared with warfarin.*
Myocardial infarction	Primary studies: 15 Interventions: 16 Events: 1,334	Low in all six domains: 2/15	Weak evidence that risk may be lower with rivaroxaban (20mg od) and higher with	Weak evidence that rivaroxaban (20mg od) and apixaban (5mg bd)	*There were no differences between*

[87] For all outcomes, some primary studies were only included in the sensitivity analyses, and not the MNAs. The results of the sensitivity analysis did not change the interpretation of the findings.
[88] Each dose and frequency of administration for a same drug were considered as distinct interventions. Each dose and frequency of administration for a drug was considered as a distinct intervention. See the full list in Sterne et al. (2017)'s report (Table 71).
[89] Standard font: evidence indirect; underlined font: evidence direct; italicised font: evidence both direct and indirect.

Outcomes	Included in the network: primary studies,[87] interventions,[88] and events	Risk of bias: number of studies/total	Summary of the network meta-analytic findings[89]		
			NOACs vs warfarin (INR 2-3)	NOACs vs NOACs	Comparisons among other interventions
		High in one or more domains: 9/15 Unclear in one or more domains, none high: 4/15	dabigatran (both 110mg and 150mg bd) and edoxaban (30mg od) when compared with warfarin.	have a lower risk compared with dabigatran (150mg bd).	*antiplatelets and warfarin.*
Major bleeding	Primary studies: 18[90] Interventions: 24 Events: 4,314	Low in all six domains: 2/18 High in one or more domains: 13/18 Unclear in one or more domains, none high: 3/18	Evidence that apixaban (5mg bd), dabigatran (110mg bd) and edoxaban (both 30 and 60mg od) may all have a lower risk than warfarin.	Evidence that rivaroxaban (20mg od) increases risk compared with apixaban (5mg bd) and edoxaban (60mg od) and that apixaban (5mg bd) may have a lower risk than dabigatran (150mg).	*Weak evidence that antiplatelets reduced the risk, compared with warfarin.*
CRB	Primary studies: 12 Interventions: 23 Events: 9,556	Low in all six domains: 2/12 High in one or more domains: 6/12 Unclear in one or more domains, none high: 4/12	Evidence apixaban (5mg bd) and edoxaban (30 and 60mg od) may all have reduced risk compared with warfarin, while edoxaban (30 and 60mg bd) may increase that risk.	Evidence that edoxaban (60mg od) and rivaroxaban (20mg od) may increase risk compared with apixaban (5mg bd) and that rivaroxaban (20mg od) may increase risk compared with edoxaban (60mg od).	Indirect evidence that antiplatelets[91] reduced the risk, compared with warfarin.
Intracranial bleeding	Primary studies: 8 Interventions: 10 Events: 757	Low in all six domains: 2/8 High in one or more domains: 3/8	Strong evidence that apixaban (5mg bd), dabigatran (both 110 and 150mg bd), edoxaban (both 30 and 60mg od) and	Weak evidence that rivaroxaban (20mg od) may be at higher risk than apixaban (5mg bd),	There were no comparisons.

[90] Seventeen studies were included in the main analysis, with the remaining study included only in sensitivity analyses
[91] At a lower than recommended dose (<150mg od)

Outcomes	Included in the network: primary studies,[87] interventions,[88] and events	Risk of bias: number of studies/total	Summary of the network meta-analytic findings[89]		
			NOACs vs warfarin (INR 2-3)	NOACs vs NOACs	Comparisons among other interventions
		Unclear in one or more domains, none high: 3/8	rivaroxaban (20mg od) have a lower risk compared with warfarin.	dabigatran (150mg bd) and edoxaban (60mg od).	
All-cause mortality	Primary studies: 18 Interventions: 15 Events: 6,479	Low in all six domains: 3/18 High in one or more domains: 11/18 Unclear in one or more domains, none high: 4/18	Evidence that apixaban (5mg bd), dabigatran (both 110 and 150mg bd), edoxaban (both 30 and 60mg od) and rivaroxaban (20mg od) may all have a lower risk compared with warfarin.	Little evidence of differences between licensed doses of NOACs.	There were no comparisons.

Appendix 13: Effectiveness, safety and cost-effectiveness review; main findings by outcome for the review on the primary prevention of VTE (Review 2)

Outcomes	Included in the network: primary studies[92], interventions[93], and events	Risk of bias: number of studies/total	Summary of the network meta-analytic findings[94]		
			NOACs vs warfarin (INR 2-3)	NOACs vs NOACs	Comparisons among other interventions
Symptomatic VTE	Primary studies: Hip 9, Knee 10, Medical conditions 4, Total 23 Interventions: Hip 13, Knee 21, Medical conditions 8 Events: Hip 231, Knee 186, Medical conditions 45	Low in all six domains: 7/23 High in one or more domains: 2/23 Unclear in one or more domains, none high: 14/23	There were no comparisons.	Hip and knee surgery: all comparisons were imprecise[95]. Medical conditions: weak evidence that the risk of symptomatic VTE may be lower with apixaban (2.5mg bd) compared with rivaroxaban (10mg od) (imprecise estimates).	Hip surgery: <u>evidence that risk may be lower with rivaroxaban (10mg od) compared with LMHW (pre-op, standard dose), and higher with LMWH (post-op, standard dose) and warfarin (INR 2–3) compared with LMWH (pre-op, standard dose)</u> (mostly imprecise estimates). Knee surgery: l<u>ittle evidence of differences in risk between apixaban (2.5mg bd), dabigatran (220mg od) or rivaroxaban (10mg od) compared with LMWH (post-op, standard dose).</u>

[92] For all outcomes, some primary studies were only included in the sensitivity analyses, and not the MNAs. The results of the sensitivity analysis did not change the interpretation of the findings.
[93] Each dose and frequency of administration for a drug was considered as a distinct intervention. See the full list in Sterne et al. (2017)'s report (Table 71).
[94] Standard font: evidence indirect; underlined font: evidence direct; italicised font: evidence both direct and indirect.
[95] Comparisons with a ratio, between the confidence interval limits, that exceeded nine were considered to be imprecise.

Outcomes	Included in the network: primary studies[92], interventions[93], and events	Risk of bias: number of studies/total	Summary of the network meta-analytic findings[94]		
			NOACs vs warfarin (INR 2-3)	NOACs vs NOACs	Comparisons among other interventions
					Medical conditions: weak evidence that risk may be lower with apixaban (2.5mg bd) compared with LMWH (standard dose)[96] (imprecise estimates).
Symptomatic DVT	Primary studies: Hip 8, Knee 9, Medical conditions 3, Total: 20 Interventions: Hip 9, Knee 24, Medical conditions 5 Events: Hip 157, Knee 81, Medical conditions 65	Low in all six domains: 6/20 High in one or more: 3/20 Unclear in one or more domains, none high: 11/20	There were no comparisons.	All comparisons were imprecise.	All comparisons were imprecise. Hip surgery: *risk higher for LMWH (post-op, standard dose) and warfarin than LMWH (pre-op, standard dose).* Knee surgery: risk higher for LMWH pre-op (standard dose) than LMWH (post-op, standard dose). Medical conditions: evidence that risk may be lower for apixaban (2.5mg bd) than LMWH (standard dose).
Symptomatic PE[97]	Primary studies: Hip 13, Knee 14, Medical conditions 3, Total 30	Low in all six domains: 6/30	There were no comparisons.	All comparisons were imprecise.	Most comparisons were imprecise. Knee surgery: some evidence that the risk may be lower with

[96] Standard dose for medical conditions.
[97] Included symptomatic non-fatal and fatal PE events where symptomatic PE was not reported.

Outcomes	Included in the network: primary studies[92], interventions[93], and events	Risk of bias: number of studies/total	Summary of the network meta-analytic findings[94]		
			NOACs vs warfarin (INR 2-3)	NOACs vs NOACs	Comparisons among other interventions
	Interventions: Hip 19, Knee 26, Medical conditions 5 Events: Hip 58, Knee 74, Medical conditions 45	High in one or more domains: 4/30 Unclear in one or more domains, none high: 20/30		Knee surgery: imprecise evidence suggested that risk may be lower for rivaroxaban (10mg od) than apixaban (2.5mg bd).	dabigatran (150mg od) and higher with apixaban (2.5mg bd), compared with LMWH (post-op, standard dose) (imprecise estimates).
Myocardial infarction	Primary studies: 9 Interventions: 11 Events: 63	Low in all six domains: 1/9 High in one or more domains: 0/9 Unclear in one or more domains, none high: 8/9	There were no comparisons.	All comparisons were imprecise.	Some evidence that risk may be lower for rivaroxaban (10mg od) than LMWH (post-op, standard dose) (imprecise estimates).
Major bleeding	Primary studies: 34 Interventions: 32 Events: 706	Low in all six domains: 9/34 High in one or more domains: 5/34 Unclear in one or more domains, none high: 20/34	There were no comparisons.	Evidence that risk may be higher with rivaroxaban (10mg od) than apixaban (2.5mg bd) and dabigatran (220mg od).	*Little evidence that the risk differed between pre-op and post-op LMWH (standard dose).* *Evidence that risk may be lower with warfarin and higher with rivaroxaban (10mg od), compared with LMWH (post-op, standard dose).*
CRB	Primary studies: 25 Interventions: 29 Events: 1,973	Low in all six domains: 8/25	There were no comparisons.	Evidence that risk may be higher for dabigatran (220mg od) and rivaroxaban (10mg od),	Evidence that risk may be higher for pre-op LMWH (standard dose) than post-op LMWH (standard dose), and higher for dabigatran

Outcomes	Included in the network: primary studies[92], interventions[93], and events	Risk of bias: number of studies/total	Summary of the network meta-analytic findings[94]		
			NOACs vs warfarin (INR 2-3)	NOACs vs NOACs	Comparisons among other interventions
		High in one or more domains: 3/25 Unclear in one or more domains, none high: 14/25		compared with apixaban (2.5mg bd).	(150mg or 220mg od) and *rivaroxaban (10mg od)* than LMWH (post-op, standard dose)[98].
All-cause mortality	Primary studies: 24 Interventions: 29 Events: 1,161	Low in all six domains: 6/24 High in one or more domains: 3/24 Unclear in one or more domains, none high: 15/24	There were no comparisons.	All comparisons were imprecise.	*Little evidence that risk is different for any intervention compared with LMWH (post-op, standard dose)*[99]*.*

[98] Note that there was statistical inconsistency between direct (significant) and indirect (not significant) estimates for rivaroxaban.
[99] Note that the direct evidence for apixaban (2.5mg bd), which indicated a (not statistically significant) reduction compared with post-op LMWH, was contrary to the indirect evidence, which suggested a statistically significant increase.

Appendix 14: Effectiveness, safety and cost-effectiveness review; main findings by outcome for the review on the acute treatment of VTE (Review 3)

Outcomes	Included in the network: primary studies, interventions[100], and events	Risk of bias: number of studies/total	Summary of the network meta-analytic findings[101]		
			NOACs vs warfarin (INR 2-3)	NOACs vs NOACs	Comparisons among other interventions
Symptomatic VTE	Primary studies: 8 Interventions: 11 Events: 728	Low in all six domains: 3/8 High in one or more domains: 3/8 Unclear in one or more domains, none high: 2/8	Evidence showed no clear difference between NOACs and warfarin.	No clear evidence of differences between NOACs.	There were no comparisons.
Symptomatic DVT	Primary studies: 9 Interventions: 13 Events: 351	Low in all domains: 4/9 High in one or more domains: 4/9 Unclear in one or more domains, none high: 1/9	Evidence showed no clear difference between NOACs and warfarin.	No clear evidence of differences between NOACs.	There were no comparisons.
Symptomatic PE	Primary studies: 9[102] Interventions: 13 Events: 300	Low in all domains: 3/9 High in one or more domains: 4/9 Unclear in one or more domains, none high: 2/9	Evidence showed no clear difference between NOACs and warfarin.	No clear evidence of differences between NOACs.	There were no comparisons.
Myocardial infarction	Primary studies: 5 Interventions: 5 Events: 57	Low in all domains: 3/5 High in one or more domains: 1/5	All comparisons were imprecise[103].	All comparisons were imprecise.	There were no comparisons.

[100] Each dose and frequency of administration for a drug was considered as a distinct intervention. See the full list in Sterne et al. (2017)
[101] Standard font: evidence indirect; underlined font: evidence direct; italicised font: evidence both direct and indirect.
[102] For eight studies, symptomatic PE events were derived by adding fatal PE and symptomatic non-fatal PE events.
[103] Comparisons with a ratio, between the confidence interval limits, that exceeded nine were considered to be imprecise

Outcomes	Included in the network: primary studies, interventions[100], and events	Risk of bias: number of studies/total	Summary of the network meta-analytic findings[101]		
			NOACs vs warfarin (INR 2-3)	NOACs vs NOACs	Comparisons among other interventions
		Unclear in one or more domains, none high: 1/5			
Major bleeding	Primary studies: 9 Interventions: 13 Events: 228	Low in all domains: 3/9 High in one or more domains: 4/9 Unclear in one or more domains, none high: 3/9	Strong evidence that risk lower with apixaban (5mg bd) and rivaroxaban (15mg bd then 20mg od), compared with warfarin.	Evidence that risk may be higher for edoxaban [60mg or 30mg (17.6%) od] and dabigatran (150mg bd) than apixaban (5mg bd).	There were no comparisons.
CRB	Primary studies: 8 Interventions: 10 Events: 2,365	Low in all domains: 3/8 High in one or more domains: 4/8 Unclear in one or more domains, none high: 1/8	Evidence that risk may be lower with apixaban (5mg bd), dabigatran (150mg bd), edoxaban [60mg or 30mg (17.6%) od] and rivaroxaban (15mg bd then 20mg od), compared with warfarin.	Evidence that risk may be higher with dabigatran (150mg bd), edoxaban [60mg or 30mg (17.6%) od] and rivaroxaban (15mg bd then 20mg od) than apixaban (5mg bd). Evidence that risk may be higher with edoxaban [60mg or 30mg (17.6%) od] and rivaroxaban (15mg bd then 20mg od) than dabigatran (150mg bd).	There were no comparisons.
All-cause mortality	Primary studies: 8 Interventions: 10 Events: 662	Low in all domains: 3/8 High in one or more domains: 4/8 Unclear in one or more domains, none high: 1/8	Little evidence showed no clear difference between NOACs and warfarin.	No clear evidence of differences between NOACs.	There were no comparisons.

Appendix 15: Effectiveness, safety and cost-effectiveness review; main findings by outcome for the review on the secondary prevention of VTE (Review 4)

Outcomes	Included in the network: primary studies, interventions,[104] and events	Risk of bias: number of studies/total	Summary of the network meta-analytic findings [105]		
			Warfarin (INR 2-3) v NOACs/placebo	NOACs vs NOACs/ placebo	Comparisons among other interventions
Symptomatic VTE	Primary studies: 10 Interventions: 9 Events: 578	Low in all six domains: 3/10 High in one or more domains: 3/10 Unclear in one or more domains, none high: 4/10	Evidence showed no clear difference between Dabigatran (150mg bd) and warfarin (all other comparisons of NOACS v warfarin were imprecise)[106]. Evidence that warfarin (INR 1.5 to 2, and 2 to 3) substantially reduced the risk, compared with placebo.	No clear evidence of differences between NOACs (all imprecise). Evidence that risk may be lower with all doses of NOACs (apixaban 2.5 and 5mg bd, dabigatran 150mg bd, and rivaroxaban 20mg od), compared with placebo.	Evidence that risk may be lower with all doses of NOACs, compared with aspirin. Evidence that aspirin substantially reduced the risk, compared with placebo.
Symptomatic DVT	Primary studies: 9 Interventions: 8 Events: 342	Low in all six domains: 2/9 High in one or more domains: 3/9 Unclear in one or more domains, none high: 4/9	No clear evidence of differences between NOACs and warfarin[107] (imprecise estimates). Evidence that warfarin may have a significantly lower risk than placebo (imprecise estimates).	No clear evidence of differences between NOACs (all imprecise). Evidence that all doses of NOACs may have a significantly lower risk than placebo.	No clear evidence that aspirin (100 mg od) reduced the risk, compared with placebo. NOACs may greatly reduce this risk, compared with aspirin.

[104] Each dose and frequency of administration for a same drug was considered as a distinct intervention. See the full list in Stern's report (Table 137).
[105] Standard font: evidence indirect; underlined font: evidence direct; italicised font: evidence both direct and indirect.
[106] Comparisons with a ratio, between the interval limits, that exceeded nine were considered to be imprecise.
[107] Direct evidence for Dabigatran (150mg bd) and indirect evidence for Apixaban (2.5mg bd, 5mg bd) Rivaroxaban (20mg od).

Outcomes	Included in the network: primary studies, interventions,[104] and events	Risk of bias: number of studies/total	Summary of the network meta-analytic findings [105]		
			Warfarin (INR 2-3) v NOACs/placebo	NOACs vs NOACs/ placebo	Comparisons among other interventions
Symptomatic PE[108]	Primary studies: 9 Interventions: 8 Events: 173	Low in all six domains: 2/9 High in one or more domains: 3/9 Unclear in one or more domains, none high: 4/9	Evidence that apixaban (2.5mg bd) had a higher risk than warfarin (imprecise estimates). Evidence that warfarin may greatly reduce the risk compared with placebo.	Weak evidence that apixaban (2.5mg bd) may have a higher risk than dabigatran (150mg bd) and rivaroxaban (20mg od) (imprecise estimates). Evidence that apixaban (2.5mg bd), dabigatran (150mg bd) and rivaroxaban (20mg od) may greatly reduce the risk compared with placebo.	Weak evidence that dabigatran (150mg bd) and rivaroxaban (20mg od) may have a lower risk than aspirin (imprecise estimates).
Myocardial infarction	Primary studies: 5 Interventions: 7 Events: 35	Low in all six domains: 3/5 High in one or more domains: 0/5 Unclear in one or more domains, none high: 2/5	All comparisons were imprecise.	All comparisons were imprecise.	All comparisons were imprecise.
Major bleeding	Primary studies: 10 Interventions: 9 Events: 87	Low in all six domains: 3/10 High in one or more domains: 3/10	Evidence that dabigatran (150mg bd) may have a lower risk than warfarin. Evidence that warfarin may increase the risk compared with placebo (imprecise estimates).	Evidence that dabigatran (150mg bd) and rivaroxaban (20mg od) may have a higher risk compared with apixaban (2.5mg and 5mg bd).	All comparisons were imprecise.

[108] Fatal and non-fatal.

Outcomes	Included in the network: primary studies, interventions,[104] and events	Risk of bias: number of studies/total	Summary of the network meta-analytic findings [105]		
			Warfarin (INR 2-3) v NOACs/placebo	NOACs vs NOACs/ placebo	Comparisons among other interventions
		Unclear in one or more domains, none high: 4/10		Evidence that rivaroxaban (20mg od) may increase the risk compared with placebo (imprecise estimates).	
CRB	Primary studies: 6 Interventions: 7 Events: 430	Low in all six domains: 2/6 High in one or more domains: 1/6 Unclear in one or more domains, none high: 3/6	Evidence that apixaban (2.5 and 5mg bd) and evidence that dabigatran (150mg bd) may have a lower risk than warfarin. Evidence that warfarin, may have a substantially higher risk than placebo.	Evidence that the risk may be lower with apixaban (2.5 and 5mg bd) than with dabigatran (150mg bd) and rivaroxaban (20mg od) (imprecise). Evidence that dabigatran (150mg od) and rivaroxaban (20mg od) may have a substantially higher risk than placebo.	Evidence that rivaroxaban (20 mg od) may have a higher risk than aspirin.
All-cause mortality	Primary studies: 9 Interventions: 9 Events: 158	Low in all six domains: 3/9 High in one or more domains: 3/9 Unclear in one or more domains, none high: 3/9	No evidence of differences between NOACs and warfarin (most imprecise).	Evidence that apixaban (5mg bd) may have lower risk than placebo (imprecise estimates).	Weak evidence that apixaban (5mg bd) may have a lower risk than aspirin (imprecise estimates).

Appendix 16: Genotyping review; generic characteristics of included reviews

Study	Search databases (year range)	Year range of synthesised studies	Total number of studies in review	Number of studies reviewed related to AF/VTE adult populations	Study types synthesised	Any other targeting
Chen et al. 2016	PubMed and Embase (no specific date limits reported)	2009 - 2014	8	7	Case-control and cohort	African descent populations
Dahal et al. 2015	MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) (inception to March 2014)	2005 - 2013	10	9	RCTs	Adult patients (≥18 years)
Franchini et al. 2014	MEDLINE (1980 to March week 1, 2014), Embase (1980 to March week 1, 2014) and Cochrane Central Register of Controlled Trials (CENTRAL)	2005 - 2013	9	9	RCTs	None
Goulding et al. 2014	MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and pharmgkb.org (January 1980 to December 2013)	2002 - 2013	15	8	RCTs	Patients from a clinical setting
Jin et al. 2014	MEDLINE and Embase (in June 2013 with verification search in July 2013)	2005 - 2013	32	25	Prospective clinical trials	None

Study	Search databases (year range)	Year range of synthesised studies	Total number of studies in review	Number of studies reviewed related to AF/VTE adult populations	Study types synthesised	Any other targeting
Shi et al. 2015	PubMed, Embase, The Cochrane library, China National Knowledge Infrastructure (CNKI), VIP, Wan-fang (from inception to March 2015) Reference lists of the relevant studies were searched for additional literature	2005 - 2013	11	8	RCTs	Patients at least 18 years old with an indication for anticoagulation
Sun et al. 2016	PubMed, Embase and CNKI (inception until August 5, 2015)	2009 - 2015	22	11	NR[109]	Asian population
Tang et al. 2015	PubMed, Embase, Web of Science, and The Cochrane Library (January 1, 2000, to March 1, 2014)	2007 - 2013	8	7	RCTs	None
Xu et al. 2014	PubMed, OVID, Cochrane Central Register of Controlled Trials (CENTRAL) (inception through to January 2014)	2005 - 2013	8	7	RCTs	None
Yu et al. 2016	PubMed, Embase, and CNKI (inception to July 19, 2015)	2005 - 2014	9	9	RCTs	Caucasian, Asian and African American patients

[109] Reviews, case reports and editorials were excluded

Appendix 17: Genotyping review; specific characteristics of included reviews

Study Author and year	Aim/objective	Characteristics of included populations	Gene polymorphism considered	Intervention/comparator	Outcomes assessed
Chen et al. 2016	To evaluate the impact of the CYP4F2 polymorphism on bleeding complications and over- anticoagulation due to coumarin	**Total**: 3,101 **Age** (mean/median: 4.8[110] to 66 **Female** (%): 41.0 to 54.7 **Ethnicity**: Caucasian, Asian, African-American	CYP4F2*3, CYP4F2*1	**VKAs**: warfarin and acenocoumarol **Dose range**: 3 to 7mg/day **Intervention**: VKA **Comparison**: CYP4F2*3 v CYP4F2*1 **Follow-up**: 3 months to 40 to 45 months	Total haemorrhage, Major haemorrhage, INR<4, Over-anticoagulation
Dahal et al. 2015	Comparison of genotype-guided dosing vs standard dosing in adult patients with various indications of warfarin use	**Total**: 2,505 **Age** (mean/median): 41.6 to 70.5yrs **Female** (%): 44.6 to 70% [majority were men] **Ethnicity**: 0 to 100% White, 0 to 35% Black and 0 to 100% Asian	CYP2C9*2 and *3 & VKORC1; CYP2C9, VKORC1 & CYP4F2	**VKAs**: warfarin **Dose range**: 2.5 to 10mg/day (of those stated) **Intervention**: genotype-guided dosing **Comparator**: standard dosing **Follow-up**: 2 weeks to 6 months	**Primary**: percentage time in therapeutic range (TTR) **Secondary**: major bleeding time to maintenance dose (TMD), supratherapeutic INR of > 4, thromboembolism, non-major bleeding, and all-cause mortality

[110] Error in text

Study Author and year	Aim/objective	Characteristics of included populations	Gene polymorphism considered	Intervention/comparator	Outcomes assessed
Franchini et al. 2014	To assess whether two approaches [genotype-guided or not] resulted in different rates of clinically relevant events such as bleeding, thrombosis and death	**Total**: 2,812 **Age** (mean/median): 64.8 v 64.3yrs (int. v control); study arms median range: 41 to 70yrs **Female** (%): 44.8 v 48.6% (int v control); study arms range: 36 to 58% **Ethnicity**: 65 to 100% White	CYP2C9; VKORC1	**VKAs**: warfarin & other VKAs **Dose range**: NR **Intervention**: genotype-guided dosing **Comparator**: standard dosing **Follow-up**: 22 to 90 days	**Primary**: incidence of major bleeding, thrombosis and death **Secondary**: time to reach a therapeutic INR; % of TTR; time to reach a stable dose; % time spent at sub-therapeutic INR, number of days in hospital

Study Author and year	Aim/objective	Characteristics of included populations	Gene polymorphism considered	Intervention/comparator	Outcomes assessed
Goulding et al. 2014	To quantify the clinical effectiveness of genotype-guided prescribing. MAIN TEXT: This study examines the current randomized controlled trial evidence for the prospective clinical use of pharmacogenetic information to improve effectiveness of drug prescribing as demonstrated by reduced harm and increased relative effectiveness. Prescribing has the potential to reduced adverse drug events and increase drug effectiveness. Our aim was to quantify the clinical effectiveness of genotype-guided prescribing	**Total**: 5,688 **Age** (mean/median): 41 to 70 years **Female** (%): 17 to 69% **Ethnicity**: 0 to 100% Caucasian, 0 to 100% Chinese, 0 to 27% Black; unspecified % Hispanic	CYP2C29; VKORC1; CYP4F2; HLA-B*5701; HIV anti-retroviral resistance mutations; TMPT; CYP2C19; CYP3A5;	**VKAs**: Warfarin, acenocoumarol/phenprocoumon; tacrolimus; clopidogrel/prasugrel/azathioprine; antiretroviral agents (12); abacavir **Dose range**: NR **Intervention**: genotype-guided dosing **Comparator**: non-genotype guided prescribing **Follow-up**: 7 days to 4 months	**Primary**: Not stated explicitly; abstract states: percentage of time in therapeutic international normalised ratio range & adverse drug events

Study Author and year	Aim/objective	Characteristics of included populations	Gene polymorphism considered	Intervention/comparator	Outcomes assessed
Jin et al. 2014	To estimate of the impact of -1639G 4 A genetic polymorphism upon warfarin dose requirement	**Total**: 5,005 **Age** (mean): 36.0 to 86.7 years **Female** (%): 12.6% to 64.9% (2 NR) **Ethnicity**: Caucasians, Asians, African population	VKORC1-1639G>A	**VKAs**: warfarin **Dose range**: NR **Intervention**: VKA **Comparator**: between genotype variation **Follow-up**: NR	**Primary**: Weighted mean maintenance dosage of warfarin
Shi et al. 2015	To determine whether genotype-guided warfarin dosing can improve clinical outcomes in comparison to conventional dosing	**Total**: 2,678 **Age** (median): 59.7 years **Female** (%): NR **Ethnicity**: NR	CYP2C9, VKORC1, CYP4F2	**VKAs**: Warfarin **Dose range**: NR **Intervention**: pharmacogenetics-based dosing of warfarin **Comparator**: conventional dosing of warfarin **Follow-up**: 28 days to 3 months	**Primary**: Time within the therapeutic range (TTR). **Secondary**: INR greater than 4, time to maintenance dose and the first target INR, adverse events during anticoagulation treatment, the frequency of major bleeding, thromboembolic events, and death from any cause

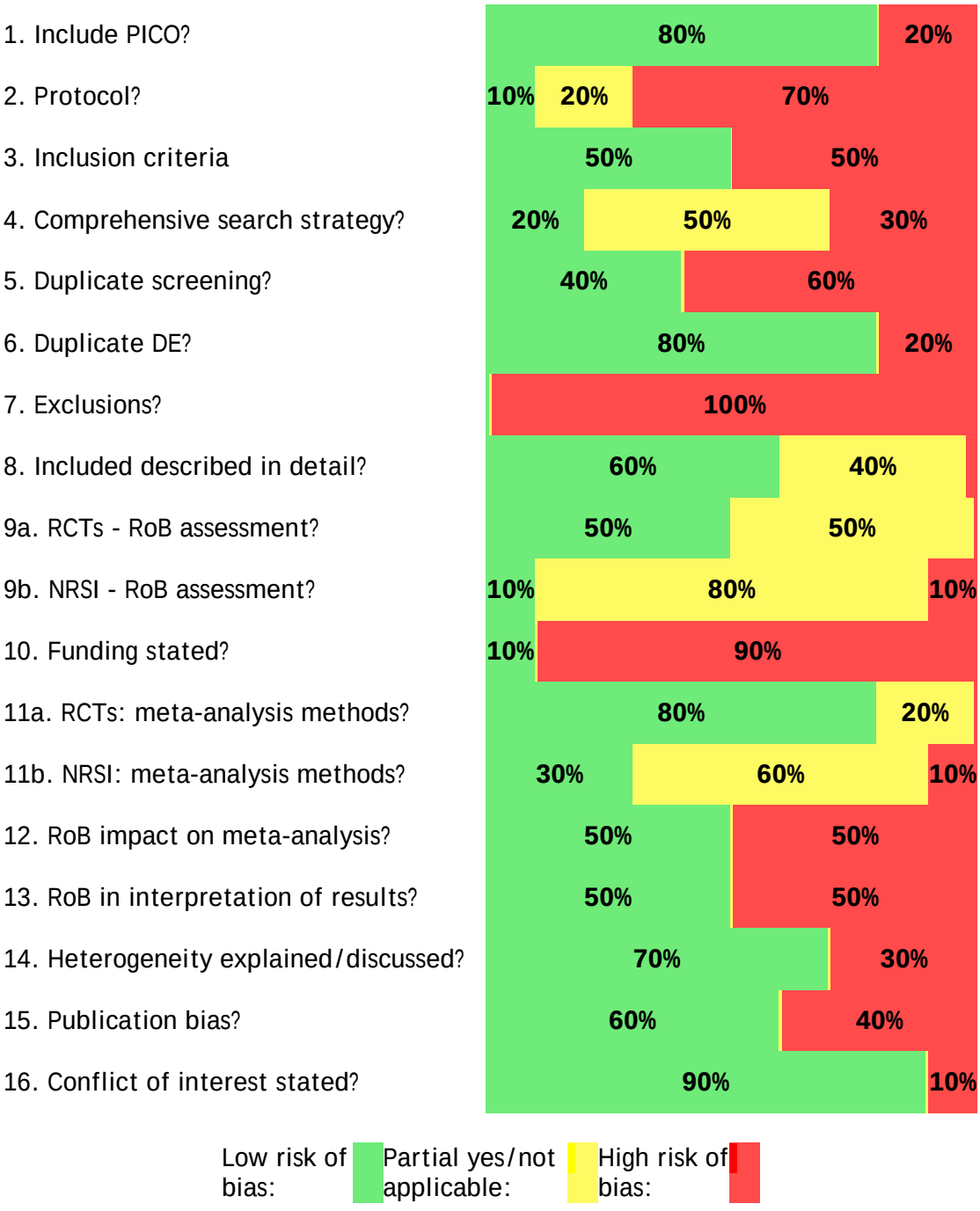
Study Author and year	Aim/objective	Characteristics of included populations	Gene polymorphism considered	Intervention/comparator	Outcomes assessed
Sun et al. 2016	To investigate the impact of the CYP4F2 polymorphism rs2108622 (p.V433M) on warfarin dose requirement	**Total**: 4,549 **Age** (mean/median): NR **Female** (%): 53.5 **Ethnicity**: Chinese, Indian, Turkish, Japanese, Korean, Asian	CYP4F2	**VKAs**: warfarin **Dose range**: 2.51 to 22.42mg/day **Intervention**: VKA **Comparison**: CT v TT v T carriers **Follow-up**: NR	**Primary**: mean difference (MD) in daily warfarin dose (MDWD) (MDs represent the relative differences in the maintenance dose due to the normalisation procedure)
Tang et al. 2015	To determine whether genotype-guided dosing of coumarin anticoagulants did not improve the percentage of time in the therapeutic INR range	**Total**: 1,805 **Age** (mean): 61.42; study arms mean range: 41.6 to 69.2 years **Female** (%): 43.1; 12 to 70% **Ethnicity**: NR	VKORC1, CYP2C9	**VKAs**: NR (coumarin anticoagulants) **Dose range**: NR **Intervention**: genotype-guided dosing **Comparator**: coumarin anticoagulants according to a non-genotype-guided dosing algorithm **Follow-up**: 58.75 (mean); 28 to 90 days (range)	**Primary**: mean difference in percentage time within the therapeutic INR range **Secondary**: major bleeding events, thromboembolic events, and INR at or greater than 4 events
Xu et al. 2014	To assess whether genotype-guided pharmacogenetic dosing of warfarin is superior to clinical dosing	**Total**: 2,098 **Age** (mean/median): NR **Female** (%): NR **Ethnicity**: NR	CYP2C9, VKORC1, CYP4F2	**VKAs**: warfarin **Dose range**: 5 to 10mg **Intervention**: genotype-guided dosing **Comparator**: clinical dosing **Follow-up**: 28 to 90 days	**Primary**: Time within the therapeutic range (TTR) **Secondary** major bleeding, minor bleeding, thromboembolic events, INR ≥ 4

Study Author and year	Aim/objective	Characteristics of included populations	Gene polymorphism considered	Intervention/comparator	Outcomes assessed
Yu et al. 2016	To show the impact of ApoE alleles on mean daily warfarin dose (MDWD). We also aimed to assess the association between ApoE alleles and the response to warfarin in different ethnic groups and to provide a reference for future warfarin pharmacogenetics studies	**Total**: 1,766 **Age** (mean/median): 42.3 to 71 years **Female** (%): 46.8%; range 34.6 to 65.5% **Ethnicity**: Caucasian, Asian and African American	Apolipoprotein E (ApoE)	**VKAs**: warfarin **Dose range**: NR **Intervention**: VKA **Comparator**: ApoE alleles E2 v E3 v E4 **Follow-up**: NR	**Primary**: The warfarin dose (mean and SD) associated with each genotype

Appendix 18: Genotyping review; risk of bias assessment of included reviews

	1	2	3	4	5	6	7	8	9a	9b	10	11a	11b	12	13	14	15	16
First author (year)	Include PICO?	Protocol?	Inclusion criteria?	Comprehensive search strategy?	Duplicate screening?	Duplicate DE?	Exclusions?	Included described in detail?	RCTs - RoB assessment?	NRSI - RoB assessment?	Funding stated?	RCTs: Appropriate meta-analysis methods?	NRSI: Appropriate meta-analysis methods?	RoB impact on meta-analysis?	RoB in interpretation of results?	Heterogeneity explanation/discussion?	Publication bias?	Conflict of interest stated?
Chen (2016)	+	-	-	-	+	-	-	PY	N/A	+	-	N/A	+	+	+	+	-	+
Dahal (2015)	+	PY	-	+	-	-	-	PY	PY	N/A	-	+	N/A	+	+	+	+	+
Franchini (2014)	+	PY	-	+	+	+	-	PY	+	N/A	-	+	N/A	-	-	-	-	+
Goulding (2015)	+	-	-	PY	+	+	-	+	+	N/A	-	+	N/A	-	-	-	-	+
Jin (2014)	-	-	-	-	-	+	-	PY	N/A	-	-	N/A	-	-	-	-	+	+
Shi (2015)	+	+	+	PY	+	+	-	+	+	N/A	+	+	N/A	+	+	+	+	+
Sun (2016)	+	-	+	PY	-	+	-	+	PY	PY	-	+	+	-	-	+	+	-
Tang (2015)	+	-	+	PY	-	+	-	+	+	N/A	-	+	N/A	+	+	+	-	+
Xu (2014)	-	-	+	-	-	+	-	+	+	N/A	-	+	N/A	-	-	+	+	+
Yu (2016)	+	-	+	PY	-	+	-	+	PY	PY	-	+	+	+	+	+	+	+

PY = partial yes, N/A = not applicable


1. Include PICO?
80%
20%
2. Protocol?
10%
20%
70%
3. Inclusion criteria
50%
50%
4. Comprehensive search strategy?
20%
50%
30%
5. Duplicate screening?
40%
60%
6. Duplicate DE?
80%
20%
7. Exclusions?
100%
8. Included described in detail?
60%
40%
9a. RCTs - RoB assessment?
50%
50%
9b. NRSI - RoB assessment?
10%
80%
10%
10. Funding stated?
10%
90%
11a. RCTs: meta-analysis methods?
80%
20%
11b. NRSI: meta-analysis methods?
30%
60%
10%
12. RoB impact on meta-analysis?
50%
50%
13. RoB in interpretation of results?
50%
50%
14. Heterogeneity explained/discussed?
70%
30%
15. Publication bias?
60%
40%
16. Conflict of interest stated?
90%
10%
Low risk of bias:
Partial yes/not applicable:
High risk of bias:

Appendix 19: Genotyping review; overlap of included primary studies within reviews

Review / Included study	Dahal (2015)	Chen (2016)	Franchini (2014)	Jin (2014)	Shi (2015)	Sun (2016)	Tang (2015)	Xu (2014)	Yu (2016)	Overlap
Anderson et al. (2007)	✓		✓		✓		✓	✓		5
Aquilante et al. (2006)				✓						
Bazan et al. (2013)				✓						
Bejarano-Achache et al. (2012)		✓								
Borgman et al. (2012)	✓		✓		✓			✓		4
Burmester et al. (2011)	✓		✓		✓		✓	✓		5
Caraco et al. (2008)	✓		✓		✓					3
Cavallri (2010)									✓	
Cerezo-Manchado et al. (2014)		✓								
Fang et al. (2014)						✓				
Gan et al. (2011)				✓						
Hillman et al. (2005)	✓		✓		✓		✓	✓		5
Hirai et al. (2015)						✓				
Jimenez-Varo et al. (2014)		✓								
John (2010)									✓	
Jonas et al. (2013)	✓		✓		✓		✓	✓		5
Kawai et al. (2014)		✓								
Kimmel (2007)									✓	

Review / Included study	Dahal (2015)	Chen (2016)	Franchini (2014)	Jin (2014)	Shi (2015)	Sun (2016)	Tang (2015)	Xu (2014)	Yu (2016)	Overlap
Kimmel at al. (2013)	✓		✓		✓		✓	✓		5
Kohnke (2005)									✓	
Krishna et al. (2014)						✓				
Kwon et al. (2011)				✓						
Lal (2007)									✓	
Lee et al. (2009)				✓		✓				2
Liang et al. (2012)				✓		✓				2
Lou et al. (2014)						✓				
Ma et al. (2012)		✓								
Miao et al. (2007)				✓						
Michaud et al. (2008)				✓						
Momary et al. (2007)				✓						
Namazi et al. (2010)				✓						
Obayashi et al. (2006)				✓						
Ohno et al. (2009)				✓						
Oliveria Almeida (2014)									✓	
Oner Ozgon et al. (2008)				✓						
Ozer et al. (2010)				✓						
Özer et al. (2013)				✓		✓				2

Review / Included study	Dahal (2015)	Chen (2016)	Franchini (2014)	Jin (2014)	Shi (2015)	Sun (2016)	Tang (2015)	Xu (2014)	Yu (2016)	Overlap
Pautas et al. (2010)				✓						
Pirmohamed et al, (2013)	✓		✓		✓		✓	✓		5
Roth et al (2014)		✓								
Santos et al. (2013)				✓						
Sconce (2006)									✓	
Sconce et al. (2005)				✓						
Shahin et al. (2011)				✓					✓	2
Sheng Wen (2011)									✓	
Shrif et al. (2011)				✓						
Singh et al. (2011)						✓				
Smires et al. (2012)				✓						
Teh et al. (2012)				✓						
Verhoef et al, (2013)							✓			
Wang et al. (2011)						✓				
Wang et al. (2012)	✓									
Yoshizawa et al. (2009)				✓						
Yuan et al. (2005)				✓						
Zhang et al. (2009)		✓								
Zhang et al. (2013)						✓				

Review **Included study**	Dahal (2015)	Chen (2016)	Franchini (2014)	Jin (2014)	Shi (2015)	Sun (2016)	Tang (2015)	Xu (2014)	Yu (2016)	Overlap
Zhu et al. (2007)				✓						
Zhu et al. (2012)						✓				

Appendix 20: Genotyping review; included and excluded references

Initially, 22 reviews were identified for possible inclusion in this overview, on the strength of their title and abstract. However, upon full-text screening, 12 studies were excluded. The main reasons for exclusion were: conference abstracts (Belley et al., 2014; Smith et al., 2015); not focusing predominantly on AF and VTE (Belley et al., 2015; Liu et al., 2015; Plumpton et al., 2016; Stergiopoulos et al., 2014; Tang et al., 2014; Tang et al., 2015); did not qualify as a systematic review (i.e. less than two databases searched) (Dahal et al., 2014; Liao et al., 2015); or did not include health or cost outcomes (Martin et al., 2017).

Reference list of included studies

Chen P, Sun Y Q, Yang G P, Li R, Pan J, and Zhou Y S. (2016). Influence of the CYP4F2 polymorphism on the risk of hemorrhagic complications in coumarin-treated patients. Saudi Medical Journal, 37, pp.361-368.

Dahal K, Sharma S P, Fung E, Lee J, Moore J H, Unterborn J N, and Williams S M. (2015). Meta-analysis of Randomized Controlled Trials of Genotype-Guided vs Standard Dosing of Warfarin. Chest, 148, pp.701-10.

Franchini M, Mengoli C, Cruciani M, Bonfanti C, and Mannucci P M. (2014). Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. Journal of Thrombosis & Haemostasis, 12, pp.1480-7.

Goulding R, Dawes D, Price M, Wilkie S, and Dawes M. (2015). Genotype-guided drug prescribing: a systematic review and meta-analysis of randomized control trials. British Journal of Clinical Pharmacology, 80, pp.868-77.

Jin B, Hong Y, Zhu J, Li Y, and Shi H M. (2014). The impact of VKORC1-1639G>A genetic polymorphism upon warfarin dose requirement in different ethnic populations. Current Medical Research & Opinion, 30, pp.1505-11.

Shi C, Yan W, Wang G, Wang F, Li Q, and Lin N. (2015). Pharmacogenetics-Based versus Conventional Dosing of Warfarin: A Meta-Analysis of Randomized Controlled Trials. PLoS ONE [Electronic Resource], 10, pp. e0144511.

Sun X, Yu W Y, Ma W L, Huang L H, and Yang G P. (2016). Impact of the CYP4F2 gene polymorphisms on the warfarin maintenance dose: A systematic review and meta-analysis. Biomedical Reports, 4, pp.498-506.

Tang T, Liu J, Zuo K, Cheng J, Chen L, Lu C, Han S, Xu J, Jia Z, Ye M, Pei E, Zhang X, and Li M. (2015). Genotype-Guided Dosing of Coumarin Anticoagulants: A Meta-analysis of Randomized Controlled Trials. Journal of Cardiovascular Pharmacology & Therapeutics, 20, pp.387-94.

Xu H, Xie X, Wang B, Chen Y, Meng T, Ma S, and Wang F. (2014). Meta-analysis of efficacy and safety of genotype-guided pharmacogenetic dosing of warfarin. International Journal of Cardiology, 177, pp.654-657.

Yu W Y, Sun X, Wadelius M, Huang L, Peng C, Ma W L, and Yang G P. (2016). Influence of APOE Gene Polymorphism on Interindividual and Interethnic Warfarin Dosage Requirement: A Systematic Review and Meta-Analysis. Cardiovascular therapeutics, 34, pp.297-307.

Reference list of excluded studies

Belley-Cote E P, Hanif H, D'Aragon F, Eikelboom J, Anderson J L, Borgman M, Jonas D E, Kimmel S, Maitland-Van Der Zee, A H, Pirmohamed M, and Whitlock R. (2014). Genotype-guided vitamin K antagonist dosing algorithms improve time in therapeutic range: A systematic review and meta-analysis. Circulation. Conference: American Heart Association's, 130, pp.

Belley-Cote E P, Hanif H, D'Aragon F, Eikelboom J W, Anderson J L, Borgman M, Jonas D E, Kimmel S E, Manolopoulos V G, Baranova E, Maitland-van der Zee, A H, Pirmohamed M, and Whitlock R P. (2015). Genotype-guided versus standard vitamin K antagonist dosing algorithms in patients initiating anticoagulation. A systematic review and meta-analysis. Thrombosis & Haemostasis, 114, pp.768-77.

Dahal K, Sharma S, and Lee J. (2014). A meta-analysis of randomized trials of genotype-guided versus standard dosing of warfarin. European Heart Journal, 35, pp.381-382.

Liao Z, Feng S, Ling P, and Zhang G. (2015). Meta-analysis of randomized controlled trials reveals an improved clinical outcome of using genotype plus clinical algorithm for warfarin dosing. Journal of Thrombosis & Thrombolysis, 39, pp.228-34.

Liu H Q, Zhang C P, Zhang C Z, Liu X C, and Liu Z J. (2015). Influence of two common polymorphisms in the EPHX1 gene on warfarin maintenance dosage: a meta-analysis. BioMed Research International, 2015, pp.564149.

Martin A, Downing J, Maden M, Fleeman N, Alfirevic A, Haycox A, and Pirmohamed M. (2017). An assessment of the impact of pharmacogenomics on health disparities: a systematic literature review. Pharmacogenomics, 18, pp.1541-1550.

Plumpton C O, Roberts D, Pirmohamed M, and Hughes D A. (2016). A Systematic Review of Economic Evaluations of Pharmacogenetic Testing for Prevention of Adverse Drug Reactions. PharmacoEconomics, 34, pp.771-793.

Smith S A. (2015). Systematic review of recent pharmacoeconomic evaluations related to genotype-guided therapy in patients at high risk for thrombotic event. Value in Health, 18 (3), pp.A142.

Stergiopoulos K, and Brown D L. (2014). Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Internal Medicine, 174, pp.1330-8.

Sun Y, Wu Z, Li S, Qin X, Li T, Xie L, Deng Y, and Chen J. (2015). Impact of gamma-glutamyl carboxylase gene polymorphisms on warfarin dose requirement: a systematic review and meta-analysis. Thrombosis Research, 135, pp.739-47.

Tang H L, Shi W L, Li X G, Zhang T, Zhai S D, and Xie H G. (2015). Limited clinical utility of genotype-guided warfarin initiation dosing algorithms versus standard therapy: a meta-analysis and trial sequential analysis of 11 randomized controlled trials. Pharmacogenomics Journal, 15, pp.496-504.

Tang W, Shi Q P, Ding F, Yu M L, Hua J, and Wang Y X. (2017). Impact of VKORC1 gene polymorphisms on warfarin maintenance dosage: A novel systematic review and meta-analysis of 53 studies. International Journal of Clinical Pharmacology & Therapeutics, 55, pp.304-321.

Appendix 21: Self-monitoring review; detailed characteristics of the studies included in the reviews

Study	Quality appraisal[111]	Study characteristics (k)	Intervention characteristics (k)	Outcome Measure
Clarkesmith et al. (2017)	Cochrane risk of bias and GRADE (Higgins and Green 2011)	**Type of studies:** RCTs **N studies reviewed** AF (11) trials (reported in twenty articles) **Sample size (total):** 2,246 **Age:** ranged from 59 to 75 years. **Gender:** NR[112] **Ethnicity:** NR[113] **Other targeting:** None **N studies reporting primary outcome** AF (6)	**Type(s) of anticoagulation**: Unspecified (6) **Intervention(s):** Education; decision aids; self-management plus education **Setting(s):** Hospital or anticoagulation clinic setting (3); general practitioner (GP); practices (2); Unspecified (1) **Follow-up:** Ranged from 3-12 months	Time in therapeutic range (TTR) Rosendaal et al. (1993) method; TTR in days; INR values in range.
Entezari-Maleki et al. (2016)	Downs and Black checklist (Downs and Black 1998). RCTs were additionally assessed using the Jadad scale (Oxford scale).	**Type of studies:** RCTs/n-RCTs **N studies reviewed:** Mixed (24)[114] **Sample size (total):** 11,607 **Age:** NR **Ethnicity:** NR **Other targeting:** None **N studies reporting primary outcome** Mixed (8)	**Type(s) of anticoagulation**: Warfarin (all) **Intervention(s):** pharmacist-managed warfarin therapy (PMWT) **Setting(s):** Pharmacist (all) **Follow-up:** 2 to 17 months	Time in therapeutic range (TTR) Rosendaal et al. (1993) methods

[111] As reported by the primary review's authors.
[112] Gender reported for each study, but not summarised by the primary review authors.
[113] Ethnicity data were tabularised for individual studies by the primary review authors (see Characteristics of included studies, in Clarkesmith et al. (2017), begins p38), but were not referred to or summarised by these authors.
[114] AF, deep vein thrombosis, pulmonary thromboembolism, or valvular heart diseases (relative proportions not reported).

Study	Quality appraisal[111]	Study characteristics (k)	Intervention characteristics (k)	Outcome Measure
Heneghan et al. (2016)	GRADE	**Type of studies**: RCTs **N studies reviewed:** 28 total (reported in 27 articles); AF (2); Valve replaced (6); Mixed (20) **Sample size (total):** 8,950 **Age:** NR **Gender:** NR **Ethnicity:** NR **Other targeting:** Long-term treatment (2mths+), any indication **N studies reporting primary outcome** Mixed/AF (22)	**Type(s) of anticoagulation**: Various[115] (mostly Warfarin) **Intervention(s):** Self-testing or self-management compared with usual care **Setting(s)[116]:** Primary care setting (11), specialist anticoagulation clinics (13); either of the settings (above) (3), data from a medical analysis laboratory (1) **Follow-up:** 2 to 57 months; mean duration was 12 months	Time in therapeutic range (TTR) Rosendaal et al. (1993) method INR values in target range
Manzoor et al. (2017)	Downs and Black checklist Downs and Black 1998	**Type of studies**: RCTs/n-RCTs **N studies reviewed:** Mixed (25)[117] **Sample size (total):** 12,252 **Age**: mean ranged from 47.4 to 81.0 years **Gender**: NR **Ethnicity:** Mainly Caucasian (4); Malay (2); Qatari (1); NR (18). **Other targeting:** None **N studies reporting primary outcome** Mixed (25)	**Type(s) of anticoagulation**: Warfarin (25) **Intervention(s):** Outpatient pharmacist-managed anticoagulation services (PMAS) compared with usual care **Setting(s):** Outpatient pharmacist (all) **Follow-up**: ranged from 3 months to four years	TTR (Rosendaal et al. (1993) interpolation method); INR values in goal INR range or given by the mean prothrombin
Sharma et al. (2015)	The Cochrane Risk of Bias	**Type of studies**: RCTs	**Type(s) of anticoagulation**: Warfarin (12); phenprocoumon and/or	TTR (% of time INR in

[115] Figures not reported
[116] Reported for all included trials only
[117] The majority of patients were treated for atrial fibrillation or venous thromboembolism (including DVT and PE) (N = 23 of 25, 92.0%).

Study	Quality appraisal[111]	Study characteristics (k)	Intervention characteristics (k)	Outcome Measure
		N studies reviewed: 26 trials (published in 45 articles) AF (2); Mixed (18)[118]; Artificial heart valve (6) **Sample size (total):** 8,763 **Age**: ranged from 16 to 91 years (+ 1 trial of children)[119] **Gender:** NR **Ethnicity:** NR **Other targeting:** Patients receiving long-term vitamin K antagonist **N studies reporting primary outcome:** AF(2); Mixed (18)	acenocoumarol and/or fluindione (6); either warfarin or phenprocoumon (1); and unspecified (1) **Intervention(s):** Self-testing or self-management compared with usual care **Setting(s):** Professionals in anticoagulant or hospital outpatient clinics (12); physician or a GP in a primary care setting (3); either of these (3); and other[120] (2) **Follow-up**: Reported as study duration, ranged from 14 weeks to more than 4 years	therapeutic range) INR values in range
Zhou et al. (2016)	The Cochrane Risk of Bias tool; GRADE	**Type of study**: RCTs (all) **N studies reviewed**: Mixed (8)[121] **Sample size (total):** 1,493 **Age** range from 57.7 to 70 years **Gender:** range from 51.2% to 68.4% male **Ethnicity:** NR **Other targeting:** None	**Type(s) of anticoagulation**: Warfarin (all) **Intervention(s):** Outpatient pharmacist-managed warfarin services (PMWS) compared with other models) **Setting(s):** Pharmacists (all) **Follow-up:** Ranged from 3 to 6 months	Time in therapeutic range

[118] Atrial fibrillation, artificial heart valves (AHVs) and venous thromboembolism were the most common clinical indications.
[119] The trial that assessed children reported a median age of 10 years.
[120] Self-testing within anticoagulant clinics
[121] The majority of patients were treated for AF, deep vein thrombosis, pulmonary thromboembolism, or valvular heart diseases (relative proportions not reported).

Study	Quality appraisal[111]	Study characteristics (k)	Intervention characteristics (k)	Outcome Measure
		N studies reporting primary outcome: Mixed (4)		

Appendix 22: Self-monitoring review; results of the included reviews by intervention type

Intervention	Conditions	Review	Number of relevant primary studies (k)[122]	Relevant primary studies	% of overlap in primary studies between reviews	Synthesis	Outcomes	Summary of Findings
Education								
Education	Education v. usual care	Clarkesmith et al. (2017)	2 RCTs (exclusive AF)	Clarkesmith et al. (2013b); Vormfelde et al. (2014)[123]	N/A	Narrative synthesis (direction of effect and statistical significance)	TTR (Rosendaal et al. (1993) interpolation method)	**Low-quality** evidence that education **may** improve TTR compared with usual care, but more studies are needed
Education plus patient decision aid (to inform preferences for anticoagulation therapy)	Education plus patient decision v. usual care	Clarkesmith et al. (2017)	1 RCT (exclusive AF)	McAlister et al. (2005)	N/A	Narrative synthesis (direction of effect and statistical significance)	Percentage of INR values in range	**Low-quality** evidence that education plus patient decision aid **may** increase the percentage of INR values in therapeutic range compared with usual care but more studies are needed
Self-monitoring								

[122] k = number of studies.
[123] Gadisseur et al. (2003) also tested education v. usual care but due to a typo in their report, the results could not be established and are, therefore, not reproduced here.

Intervention	Conditions	Review	Number of relevant primary studies (k)[122]	Relevant primary studies	% of overlap in primary studies between reviews	Synthesis	Outcomes	Summary of Findings
Self-testing (with guidance on dosing from a clinician)	**Self-testing** v. usual care	Sharma et al. (2015) Heneghan et al. (2016)	1 RCT (exclusive AF)	Khan et al. (2004)	100%	Narrative synthesis (direction of effect and statistical significance)	TTR (% of time INR in therapeutic range)	**Low-quality** evidence that there is no difference between **self-testing** on improving time INR in therapeutic range compared with usual care, but more studies are needed
		Mixed population (% time in therapeutic range)						
		Sharma et al. (2015)	5 RCTs	Azarnoush et al. (2011); Christensen (2011); Gadisseur et al. (2003); Khan et al. (2004); Matchar et al. (2010)	43%	Data meta-analysed	TTR (% of time INR in therapeutic range)	**Low-quality** evidence that **self-testing** may modestly improve the percentage of time INR is in the therapeutic range, compared with usual care but more studies are needed
		Heneghan et al. (2016)	7 RCTs	Beyth et al. (2000); Christensen et al. (2011); Gardiner et al. (2005); Kaatz et al. (unpublished); Khan et al. (2004); Matchar et		Narrative synthesis (direction of effect and statistical significance	TTR (Rosendaal et al. (1993) interpolation method)	Mixed, **moderate-quality** evidence for **self-testing** with three trials reporting longer TTR and four trials reporting

Intervention	Conditions	Review	Number of relevant primary studies (k)[122]	Relevant primary studies	% of overlap in primary studies between reviews	Synthesis	Outcomes	Summary of Findings
				al. (2010); Rasmussen et al. (2012)				shorter TTR, compared with usual care
		Mixed population (% values in therapeutic range)						
		Sharma et al. (2015)	2 RCTs	Christensen (2011); Gadisseur et al. (2003)	0%	Narrative synthesis (direction of effect and statistical significance)	INR values in range	**Low-quality** evidence that **self-testing** may improve the number of INR values in the therapeutic range, compared with usual care though more studies are needed
		Heneghan et al. (2016)	2 RCTs	Kaatz et al. (unpublished); White et al. (1989)		Narrative synthesis (direction of effect and statistical significance)		**Moderate-quality** evidence that **self-testing** may enhance the mean percentage of INR values in target range, compared with control but more studies are needed
Self-management (self-testing and treatment	Education plus self-	Clarkesmith et al. (2017)	2 RCTs (exclusive AF)	Christensen et al. (2007); Gadisseur et al. (2003)	N/A	Data meta-analysed	TTR (Rosendaal et al. (1993)	**Low-quality** evidence favoured the education plus **self-management**

Intervention	Conditions	Review	Number of relevant primary studies (k)[122]	Relevant primary studies	% of overlap in primary studies between reviews	Synthesis	Outcomes	Summary of Findings
according to an algorithm)	management[124] v. usual care						interpolation method)	intervention group among AF populations, in terms of TTR compared with usual care, but was not statistically significant. More studies are needed
	Self-management v. usual care	Sharma et al. (2015); Heneghan et al. (2016); Clarkesmith et al. (2017)	1 RCT (exclusive AF)	Voller et al. (2005)	100%	Narrative synthesis (direction of effect and statistical significance)	TTR (Cumulative days)	**Low-quality** evidence that among AF populations, **self-management** increases TTR, compared with usual care, but more studies are needed
		Mixed population (% time in therapeutic range)						
		Sharma et al. (2015)	6 RCTs	Menendez-Jandula et al. (2005); Fitzmaurice et al. (2005); Verret et al. (2012); Fitzmaurice et al. (2002); Gadisseur et	67%	Data meta-analysed	TTR (% of time INR in therapeutic range)	**Low-quality** evidence that **self-management has little effect on** TTR, compared with usual care. More high-

[124] Clarkesmith et al. (2017) use the term self-testing but the description of the intervention is consistent with our use of the term self-management hence this label will be used from herein for this intervention

Intervention	Conditions	Review	Number of relevant primary studies (k)[122]	Relevant primary studies	% of overlap in primary studies between reviews	Synthesis	Outcomes	Summary of Findings
				al. (2003); Sunderji et al. (2004)				quality studies are needed
		Heneghan et al. (2016)	8 RCTs	Fitzmaurice et al. (2002); Fitzmaurice et al. (2005); Sunderji et al. (2004); Menendez-Jandula et al. (2005); Siebenhofer et al. (2007); Christensen et al. (2006); Grunau et al. (2011); Verret et al. (2012)		Narrative synthesis (direction of effect and statistical significance)	TTR (Rosendaal et al. (1993) interpolation method)	Mixed, **moderate-quality** evidence for **self-management** with three trials reporting longer TTR and three trials reporting shorter TTR compared with usual care
		Mixed population (% values in therapeutic range)						
		Sharma et al. (2015)	7 RCTs	Cromheecke et al. (2000); Fitzmaurice et al. (2002); Fitzmaurice et al. (2005); Menendez-Jandula et al. (2005); Sawicki (1999); Voller et al. (2005); Gadisseur et al. (2003)	63%	Narrative synthesis (direction of effect and statistical significance)	INR values in range	Mixed **low-quality** evidence for **self-management intervention** with five trials reporting higher and two trials reporting lower percentages of INR values in therapeutic range compared with usual care

Intervention	Conditions	Review	Number of relevant primary studies (k)[122]	Relevant primary studies	% of overlap in primary studies between reviews	Synthesis	Outcomes	Summary of Findings
		Heneghan et al. (2016)	8[125] RCTs	Cromheecke et al. 2000; Fitzmaurice et al. (2002); Grunau et al. (2011); Menendez-Jandula et al. (2005); Sawicki (1999); Siebenhofer et al. (2007); Sunderji et al. (2004); Voller et al. (2005)		Narrative synthesis (direction of effect and statistical significance)		**Moderate-quality** evidence that **self-management** may enhance the mean percentage of INR values in target range, compared with control
Pharmacist-managed anticoagulation services								
Pharmacist-managed anticoagulation services (PMAS)	Pharmacist-managed anticoagulation services (PMAS) compared with usual care	Manzoor et al. (2017)	3 RCTs + 22 n-RCTs	RCTs: Chan et al. (2006); Wilson et al. (2003); Bungard et al. (2012) n-RCTs: Bungard et al. (2009); Chamberlain et al. (2001); Chiquette et al. (1998); Cohen et al. (1985); Duran-Parrondo et al. (2011); Elewa et al. (2016); Garabedian-	31%	Narrative synthesis (direction of effect and statistical significance)	TTR (Rosendaal et al. (1993) interpolation method; k = 19); INR values in goal INR range (k = 5) or given by the mean prothrombin (PT; k = 1)	Evidence that the quality of anticoagulation may be better in the PMAS, compared with usual care. However, the q**uality** of the evidence is **uncertain**

[125] Gadisseur et al. (2003) not included as separate data for self-testing and self-management not reported.

Intervention	Conditions	Review	Number of relevant primary studies (k)[122]	Relevant primary studies	% of overlap in primary studies between reviews	Synthesis	Outcomes	Summary of Findings
				Ruffalo et al. (1985)[126]; Garwood et al. (2008); Gray et al. (1985); Gupta et al. (2015); Hall et al. (2011); Harrison et al. (2015); Hasan et al. (2011); Holden and Holden (2000); Motycka et al. (2012)[126]; Patel-Naik et al. (2010); Poon et al. (2007); Rudd and Dier (2010); Saokaew et al. (2012); Thanimalai et al. (2013); Witt et al. (2005); Young et al. (2011)				
Pharmacist-managed warfarin therapy (PMWT)	Pharmacist-managed warfarin therapy (PMWT) compared with usual care	Entezari-Maleki et al. (2016)	3 RCTs	Lalonde et al. (2008); Wilson et al. (2003); Bungard et al. (2012)		Data pooled but not weighted	TTR (Rosendaal et al. (1993) interpolation method)	Evidence that PMWT may improve TTR, compared with usual care. However, the q**uality** of the evidence is **uncertain**

[126] Not mixed AF/VTE population (population not reported)

Intervention	Conditions	Review	Number of relevant primary studies (k)[122]	Relevant primary studies	% of overlap in primary studies between reviews	Synthesis	Outcomes	Summary of Findings
			5 n-RCTs	Rudd and Dier (2010); Witt et al. (2005); Bungard et al. (2009); Hall et al. (2011); Young et al. (2011)		Data pooled but not weighted	TTR (Rosendaal et al. (1993) interpolation method)	Evidence that PMWT may improve TTR compared with usual care. However, the q**uality** of the evidence is **uncertain**
	Pharmacist-managed warfarin therapy (PMWT) v. physicians, nurses and other healthcare professionals providing management or usual care	Zhou et al. (2016)	4 RCTs	Bungard et al. (2012); Lalonde et al. (2008); Verret et al. (2012); Wilson et al. (2003)		Data meta-analysed	TTR (Rosendaal et al. (1993) interpolation method)	**High-quality** evidence that PMWT may improve TTR compared with usual care

Appendix 23: Self-monitoring review; summary of studies included by the reviews

Study Author and year	Topic Focus	Search + Year range of synthesised studies	Total number of studies reviewed	Number of studies reviewed related to AF/VTE adult populations and TTR outcome	Study types synthesised
Clarkesmith et al. (2017)	Adherence	**Search:** Update of review first published in 2013[127]. Databases searched in February 2016. **Year range of included studies:** 1999 to 2014.	11 (reported in twenty articles)	11 (AF)	RCTs
Entezari-Maleki et al. (2016)	Adherence	**Search:** database inception to January2014 **Year range of included studies:** 1995 to 2013.	24 (mixed conditions)	8 (mixed conditions)	RCTS (3) n-RCTs (5)
Heneghan et al. (2016)	Adherence	**Search:** Update of review published in 2010. Databases searched in July, 2015. **Year range of included studies:** 1989 to 2012.	28	20 (mixed conditions; 2 AF)	RCTs

[127] The authors searched the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE) in The Cochrane Library (2012, Issue 7 of 12), MEDLINE Ovid (1950 to week 4 July 2012), EMBASE Classic + EMBASE Ovid (1947 to Week 31 2012), PsycINFO Ovid (1806 to 2012 week 5 July) on 8 August 2012 and CINAHL Plus with Full Text EBSCO (to August 2012) on 9 August 2012.

Study Author and year	Topic Focus	Search + Year range of synthesised studies	Total number of studies reviewed	Number of studies reviewed related to AF/VTE adult populations and TTR outcome	Study types synthesised
Manzoor et al. (2017)	Adherence	**Search:** Database inception to May 2017. **Year range of included studies:** 1985 to 2016.	25	25 (mixed mostly AF/VTE)	RCTs (3), non-randomised controlled trials (22)
Sharma et al. (2015)	Adherence	**Search:** Update of existing Cochrane review[128] published in 2010. Databases searched from 2007 to May 2013[129] **Year range of included studies:** 1996 to 2012.	26 (reported in 45 articles)	2 (AF) 18 (Mixed various)	RCTs
Zhou et al. (2016)	Adherence	**Search:** From inception to July 31, 2015. **Year range of included studies:** 2003 to 2013.	8 (mixed conditions)	4 (mixed conditions)	RCTS

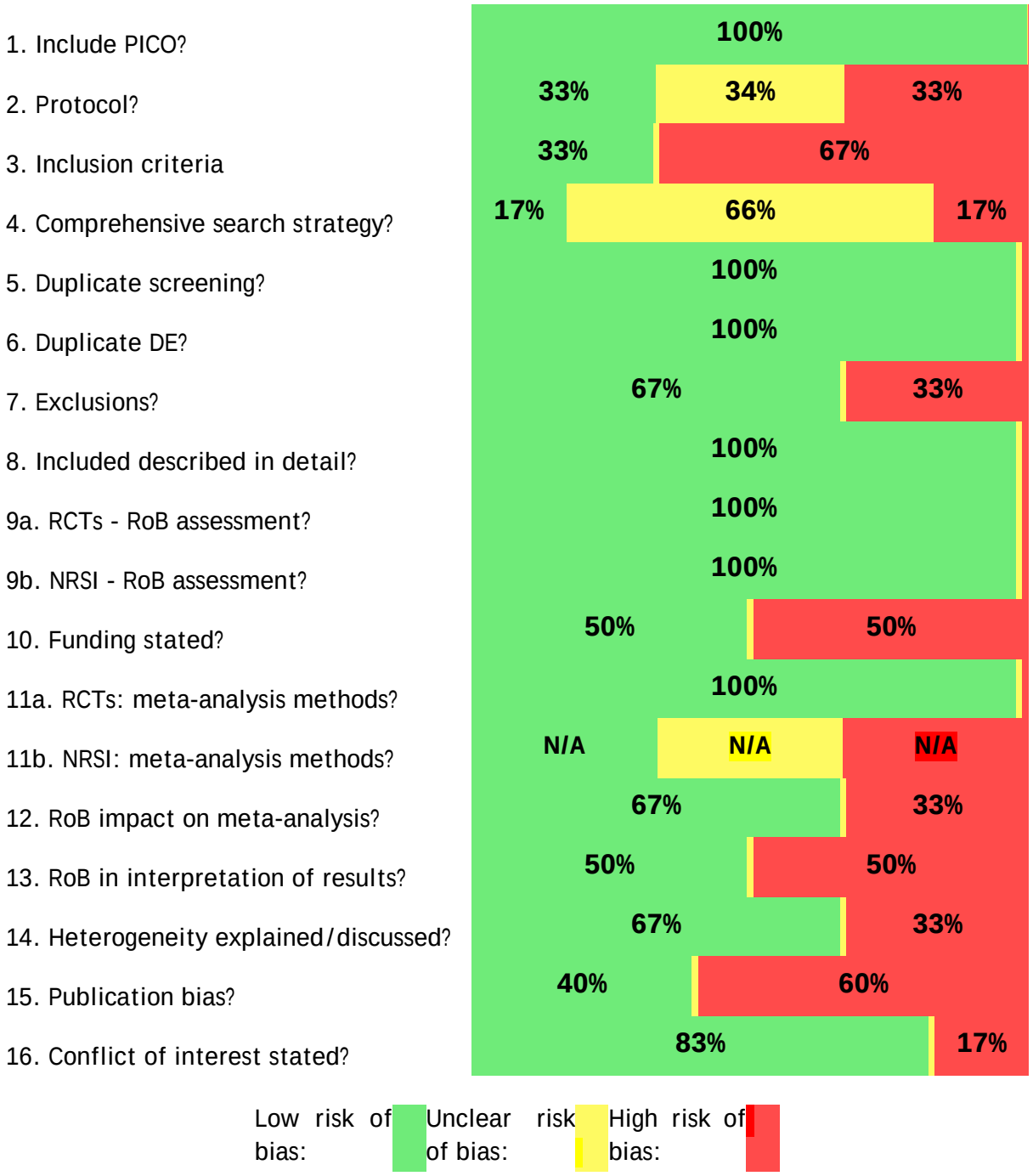
[128] Garcia-Alamino JM, Ward AM, Alonso-Coello P, Perera R, Bankhead C, Fitzmaurice D, et al. Self-monitoring and self-management of oral anticoagulation. Cochrane Database Syst Rev 2010;4:CD003839.
[129] Original review searched major databases searched from inception to 2007

Appendix 24: Self-monitoring review; risk of bias assessment of included reviews

	1	2	3	4	5	6	7	8	9a	9b	10	11a	11b	12	13	14	15	16
First author (year)	Include PICO?	Protocol?	Inclusion criteria	Comprehensive search strategy?	Duplicate screening?	Duplicate DE?	Exclusions?	Included described in detail?	RCTs - RoB assessment?	NRSI - RoB assessment?	Funding stated?	RCTs: Appropriate meta-analysis methods?	NRSI: Appropriate meta-analysis methods?	RoB impact on meta-analysis?	RoB in interpretation of results?	Heterogeneity explanation/discussion?	Publication bias?	Conflict of interest stated?
Clarkesmith (2017)	+	+	-	+	+	+	+	+	+	N/A	+	+	N/A	+	+	+	+	+
Entezari-Maleki (2016)	+	-	-	PY[130]	+	+	+	+	+	+	-	N/A[131]	N/A	N/A	-	+	-	+
Heneghan (2016)	+	+	-	PY[132]	+	+	+	+	+	N/A	+	N/A	N/A	N/A	-	-	N/A	+
Manzoor (2017)	+	PY[133]	-	PY	+	+	-	+	+	+	-	N/A	N/A	N/A	-	-	N/A	+
Sharma (2015)	+	PY	+	PY	+	+	+	+	+	N/A	+	+	N/A	-[134]	+	+	-	+
Zhou (2016)	+	-	+	-[135]	+	+	-	+	+	N/A	-	+	N/A	+	+	+	-	-

PY = partial yes, N/A = not applicable

[130] There was no search of the grey literature.
[131] The means were pooled, but no meta-analysis weighted by sample size was conducted.
[132] Searches were updated in July 2015, less than 24 months before publication.
[133] The protocol was given, but the authors did not state whether there were any deviations from the protocol.
[134] Risk of bias was considered for other analyses, but not for time in therapeutic range (TTR).
[135] Did not justify the restriction of the searches to English-language journal articles.


1. Include PICO?
2. Protocol?
3. Inclusion criteria
4. Comprehensive search strategy?
5. Duplicate screening?
6. Duplicate DE?
7. Exclusions?
8. Included described in detail?
9a. RCTs - RoB assessment?
9b. NRSI - RoB assessment?
10. Funding stated?
11a. RCTs: meta-analysis methods?
11b. NRSI: meta-analysis methods?
12. RoB impact on meta-analysis?
13. RoB in interpretation of results?
14. Heterogeneity explained/discussed?
15. Publication bias?
16. Conflict of interest stated?
100%
33%
34%
33%
33%
67%
17%
66%
17%
100%
100%
67%
33%
100%
100%
100%
50%
50%
100%
N/A
N/A
N/A
67%
33%
50%
50%
67%
33%
40%
60%
83%
17%
Low risk of bias:
Unclear risk of bias:
High risk of bias:

Appendix 25: Self-monitoring review; overlap in primary studies

Review / Included Studies	Clarkesmith (2017)	Entezari-Maleki (2016)	Heneghan (2016)	Manzoor (2017)	Sharma (2015)	Zhou (2016)	Overlap
Education							
Clarkesmith et al. (2013b)	✓						
Vormfelde et al. (2014)	✓						
Education plus decision aid							
McAlister et al. (2005)	✓						
Self-testing (% time in therapeutic range)							
Azarnoush et al. (2011)					✓		
Beyth et al. (2000)			✓				
Christensen et al. (2011)			✓		✓		2
Gadisseur et al. (2003)	✓				✓		2
Gardiner et al. (2005)			✓				
Kaatz et al. (unpublished)			✓				
Khan et al. (2004)			✓		✓		2
Matchar et al. (2010)			✓		✓		2
Rasmussen et al. (2012)			✓				
Self-testing (% values in therapeutic range)							
Christensen et al. (2011)					✓		
Gadisseur et al. (2003)					✓		
Kaatz et al. (unpublished)			✓				
White et al. (1989)			✓				
Self-management plus education							
Christensen et al. (2007)	✓						

Review / Included Studies	Clarkesmith (2017)	Entezari-Maleki (2016)	Heneghan (2016)	Manzoor (2017)	Sharma (2015)	Zhou (2016)	Overlap
Gadisseur et al. (2003)	✓						
Self-management (AF only, days in therapeutic range)							
Voller et al. (2005)			✓		✓		2
Self-management (mixed population, % time in therapeutic range)							
Christensen et al. (2006)			✓				
Fitzmaurice et al. (2002)			✓		✓		2
Fitzmaurice et al. (2005)			✓		✓		2
Gadisseur et al. (2003)					✓		
Grunau et al. (2011)			✓				
Menendez-Jandula et al. (2005)			✓		✓		2
Siebenhofer et al. (2007)			✓				
Sunderji et al. (2004)			✓		✓		2
Verret et al. (2012)			✓		✓		2
Self-management (mixed population, % values in therapeutic range)							
Cromheecke et al. (2000)					✓		
Fitzmaurice et al. (2002)			✓		✓		2
Fitzmaurice et al. (2005)					✓		
Gadisseur et al. (2003)					✓		
Grunau et al. (2011)			✓				
Menendez-Jandula et al. (2005)			✓		✓		2
Sawicki (1999)			✓		✓		2
Siebenhofer et al. (2007)			✓				
Sunderji et al. (2004)			✓				
Voller et al. (2005)			✓		✓		2

Review / Included Studies	Clarkesmith (2017)	Entezari-Maleki (2016)	Heneghan (2016)	Manzoor (2017)	Sharma (2015)	Zhou (2016)	Overlap
Pharmacist-managed warfarin therapy							
Bungard et al. (2009)		✓		✓			2
Bungard et al. (2012)		✓		✓		✓	3
Chamberlain et al. (2001)				✓			
Chan et al. (2006)				✓			
Chiquette et al. (1998)				✓			
Cohen et al. (1985)				✓			
Duran-Parrondo et al. (2011)				✓			
Elewa et al. (2016)				✓			
Garabedian-Ruffalo et al. (1985)[136]				✓			
Garwood et al. (2008)				✓			
Gray et al. (1985)				✓			
Gupta et al. (2015)				✓			
Hall et al. (2011)		✓		✓			2
Harrison et al. (2015)				✓			
Hasan et al. (2011)				✓			
Holden and Holden (2000)				✓			
Lalonde et al. (2008)		✓				✓	2
Motycka et al. (2012)[126]				✓			
Patel-Naik et al. (2010)				✓			
Poon et al. (2007)				✓			

[136] Not mixed AF/VTE population (population not reported)

Review **Included Studies**	Clarkesmith (2017)	Entezari-Maleki (2016)	Heneghan (2016)	Manzoor (2017)	Sharma (2015)	Zhou (2016)	Overlap
Rudd and Dier (2010)		✓		✓			2
Saokaew et al. (2012)				✓			
Thanimalai et al. (2013)				✓			
Verret et al. (2012)						✓	
Wilson et al. (2003)		✓		✓		✓	3
Witt et al. (2005)		✓		✓			2
Young et al. (2011)		✓		✓			2

Appendix 26: Reviews of stakeholder experiences; characteristics of included reviews

Author, Year Quality rating (QR) Aims	Review characteristics	Themes
Alamneh et al. (2016) **QR** 7/11 **Aims** to evaluate current practices of anticoagulation in AF, pharmacologic features and adoption patterns of NOACs, their impacts on proportion of eligible patients who receive oral anti-coagulants, persisting challenges and future prospects for optimal anticoagulation.	**Population:** Patients with AF **Drug(s):** Warfarin NOACs (not further specified) **Number of included primary studies:** N=140 included studies, unknown number of participants **Type of included primary studies:** - prospective and retrospective - observational studies - review articles - meta-analyses, - RCTs, - experimental (in vivo and in vitro studies) - published AF treatment guidelines **Quality assessment of primary studies**: Not reported	**Perceptions and Attitudes** ***Patients*** The lack of a specific reversal agent has been a major concern among prescribers and patients, ultimately affecting adoption into clinical practice Major uncertainties related to NOACs include medication adherence and persistence, absence of specific antidote for most NOACs, higher cost, and lack of data in some groups of patients in which they've not been adequately studied There are some concerns that patients may have difficulty in remembering to take NOACs without the requirement of blood monitoring (INR monitoring) ***Practitioner*** NOAC adoption trends are quite variable, with slow integration into clinical practice reported in most countries; there has been a limited impact to date on prescribing practice.
Clarkesmith et al. (2017) **QR** 10/11	**Population:** Patients with AF receiving oral anticoagulation therapy **Drug(s):** Warfarin	**Behaviour and Uptake** ***Patients*** We found small but positive effects of education on anxiety [GB: HADS score=QOL] (MD-0.62, 95% CI -1.21 to -0.04, Isqu0%, 2

Author, Year **Quality rating (QR)** **Aims**	**Review characteristics**	**Themes**
Aims to evaluate the effects of educational and behavioural interventions for oral anticoagulation therapy. (OAT) on TTR in patients with AF.	**Number of included primary studies:** N=11 included studies, 2,246 participants **Type of included primary studies:** **-** RCTs **Quality assessment of primary studies:** Cochrane risk of bias tool	trials, 587 participants, low quality evidence) and depression (MD -0.74, 95% CI -1.34 to -0.14, Isqu 0%, 2 trials, 587 participants, low quality evidence) compared with usual care over 12 months. Pooled data for the AF patients demonstrated that self-monitoring plus education did not significantly improve TTR when compared to usual care (MD 6.3, 95% CI -5.63 to 18.25. AF cohort, self- monitoring is no more successful in increasing INR control than usual care. Using decision aids didn't have a significant impact on AF patients' anxiety levels (Thomson 2007) or patient satisfaction (Man-Son-Hing 1999). Clarkesmith (2013) found decline in both anxiety and depression in groups at the 6 month follow-up. Patients may feel more anxious and depressed in the initial months following diagnosis and treatment commencement. This suggests that patients that took part in the decision aid trial were uncertain as to which treatment they were going to choose.
Entezari-Maleki et al. (2016) **QR** 9/11 **Aims** to perform a systematic review of literature to compare pharmacist-managed warfarin therapy (PMWT) with usual medical care (UMC)	**Population:** Patients receiving warfarin therapy **Condition:** AF common to all included studies; but some also included patients with DVT, PE, myocardial infarction, heart valve replacement **Drug(s):** Warfarin **Number of included primary studies:**	**Behaviour and Uptake** ***Patients*** All patients in PMWT and 55% of UMC group preferred the PMWT group for future OAC management. The study supported PMWT regarding cost saving and patient satisfaction, results showed that PMWT model is superior to UMC in managing warfarin therapy based on observational studies. As well, it is comparable to UMC based on RCT studies. Patients believe that the pharmacists were more expert in AC control compared with their physicians' -'high satisfaction' of patients and 'high insights from pharmacists'

Author, Year **Quality rating (QR)** **Aims**	**Review characteristics**	**Themes**
	N=24 included studies (of which 6 reported relevant findings); 11,607 participants **Type of included primary studies:** - RCTs and non-RCTs **Quality assessment of primary studies:** Jadad scale	A literature review showed that impact of PMWT service in improving quality of life of patients with oral anticoagulation therapy was documented in a very limited number of studies. In a Lalonde et al report, health-related quality of life was similar between PMWT and UMC.
Loewen et al. (2017) **QR** 10/11 **Aims** To provide clinicians, guideline developers and policy-makers with insights into values and preferences of AF patients for stroke prevention therapy and patient specific factors which affect those values and preferences.	**Population:** Patients requiring antithrombotic therapy in AF **Drug(s):** NOACs **Number of included primary studies:** N=25 included studies; 641 participants **Type of included primary studies:** **-** Discrete choice experiments **Quality assessment of primary studies:** CONSORT STROBE COREQ ISPOR	**Preferences and Choices** ***Patients*** Across all SPAF antithrombotic therapy options, stroke prevention efficacy is the most important value. After efficacy and safety, one versus two daily doses, antidote availability, absence of dietary restrictions and drug-drug interactions are of intermediate and variable importance. Preferences for INR testing or no INR testing are largely unpredictable; Prior stroke, bleed or OAC use does not affect patient values significantly, although prior experience with warfarin increases preference for warfarin over no therapy and for INR testing over no INR testing. Treatment choices are unpredictable, probably due to latent beliefs and framing effects. Preferences for NOAC over warfarin are highly variable and published studies are susceptible to bias based on sponsorship. Preferences for NOAC over warfarin are overwhelmed by even small increases in out-of-pocket drug cost. From the available

Author, Year Quality rating (QR) Aims	Review characteristics	Themes
		evidence there is no substitute for directly clarifying patients' actual values and preferences related to attributes of SPAF antithrombotic therapy (e.g. stroke risk, bleeding risk, cost of therapy, number of daily doses, need for regular blood testing, drug-drug interactions, dietary restrictions, lifestyle implications, antidote availability). Cultural or familial attitudes and personal experiences are latent sources of inter-individual variability in values and preferences and may include stigma of taking medication, perceptions of cost and risk aversion, among others.
Mas Dalmau et al. (2017) **QR** 10/11 **Aims** to evaluate and synthesize patients' and physicians' perceptions and attitudes towards the benefits and downsides of vitamin K antagonist, in order to explore potential factors related with its underuse	**Population:** Patients with AF and physicians who treat these patients **Drug(s):** VKAs **Number of included primary studies:** N=9 included studies; 250 patients and 91 physicians **Type of included primary studies:** **-** qualitative or mixed-methods studies **Quality assessment of primary studies:** CASP tool	**Perceptions and Attitudes** ***Patients*** While patients noted the lack of information and under- standing of VKAs therapy as their main concerns it was often inadequately provided and insufficient. Balance of interests and downsides (patients: assurance of treatment success, stroke prevention and longer life; risk of stroke perceived or conditions associated with anticoagulation understood; basing opinions on friends/family experiences; sceptical if perception that treatment was ineffective, never had stroke or first time in therapy) Three additional themes were of interest to patients: knowledge and understanding, impact on daily life, and satisfaction with therapy. Patients' experiences suggested a mix of a paternalistic and an interpretative model (the physician take the decision, considering the patient's values and preferences)

Author, Year Quality rating (QR) Aims	Review characteristics	Themes
		Patients believed they were ignorant and delegated decision management to professional; belief that emergency circumstances prevented patient decision management. Impact on daily life, factors concerning, dietary, drug alcohol restrictions, bruises, activity limitations, monitoring as calming, routine, and as a burden. Satisfaction with therapy (improved when info given individually and focused on care; dissatisfied when lack of information, quality and level of info provided by GPs, difficulties and costs r/t monitoring, HCPs lack of knowledge of patient's medical history). ***Practitioner*** Roles in decision-making and therapy management [doctors: support SDM, degree of perceived appropriate patient involvement varies, negotiating delegation by patient, delegating to specialist, belief in patient-centred versus disease-centred DM, perceived difficulties communicating with other HCPs, psychosocial characteristics of patients] Physicians regard uncertainty in specific cases, the need of individualized decision-making, and the delegated responsibility in decision making as the main difficulties for using VKAs. Information to reinforce anticoagulation use, balance of benefits and downsides, roles in decision-making and therapy management. Despite the availability of guidelines and research evidence, some physicians considered that this information did not always clarify their doubts in a treatment with narrow therapeutic

Author, Year Quality rating (QR) Aims	Review characteristics	Themes
		margins. They identified ambiguities in some of the guidelines, and stated that the included populations were not necessarily representative of the very elderly, the main candidates for therapy. Moreover, it is crucial to improve the quality of the information provided to patients because it is the main factor of dissatisfaction with the therapy. In one study some family physicians felt that specialized physicians delegated the responsibility of decision making to them. These two sources of delegation were perceived by family physicians as a burden. The feeling of family physicians that specialized physicians delegated the responsibility of decision making to them could be explained by the lacking certainty about the treatment and the inadequate exchange of information between them.
Pandya et al. (2017) **QR** 7/11 **Aims** to identify the factors underpinning patients' non-adherence to anticoagulants in atrial fibrillation (AF), and subsequently contemplates to what extent the NOACs might overcome the known	**Population:** Patients taking oral anticoagulants for AF **Drug(s):** Warfarin and NOACs **Number of included primary studies:** N=47 included studies; 4,151 participants **Type of included primary studies:** **-** Surveys - Interviews - Discrete choice experiments	**Perceptions and Attitudes** ***Patients*** This review highlights patients' lack of understanding regarding AF and stroke, and the importance of anticoagulant therapy (in any form) on stroke prevention. This understanding is integral to facilitating adherence, as well as for engaging patients in decision-making. Factors negatively affecting patients' day-to-day lives (especially regular therapeutic drug monitoring, dose adjustments, and dietary considerations) predominantly underpin a patient's reluctance to take warfarin therapy, leading to non-adherence. Absence of regular monitoring, limited access to antidotes, high costs of the medications, twice-daily dosing (dabigatran and

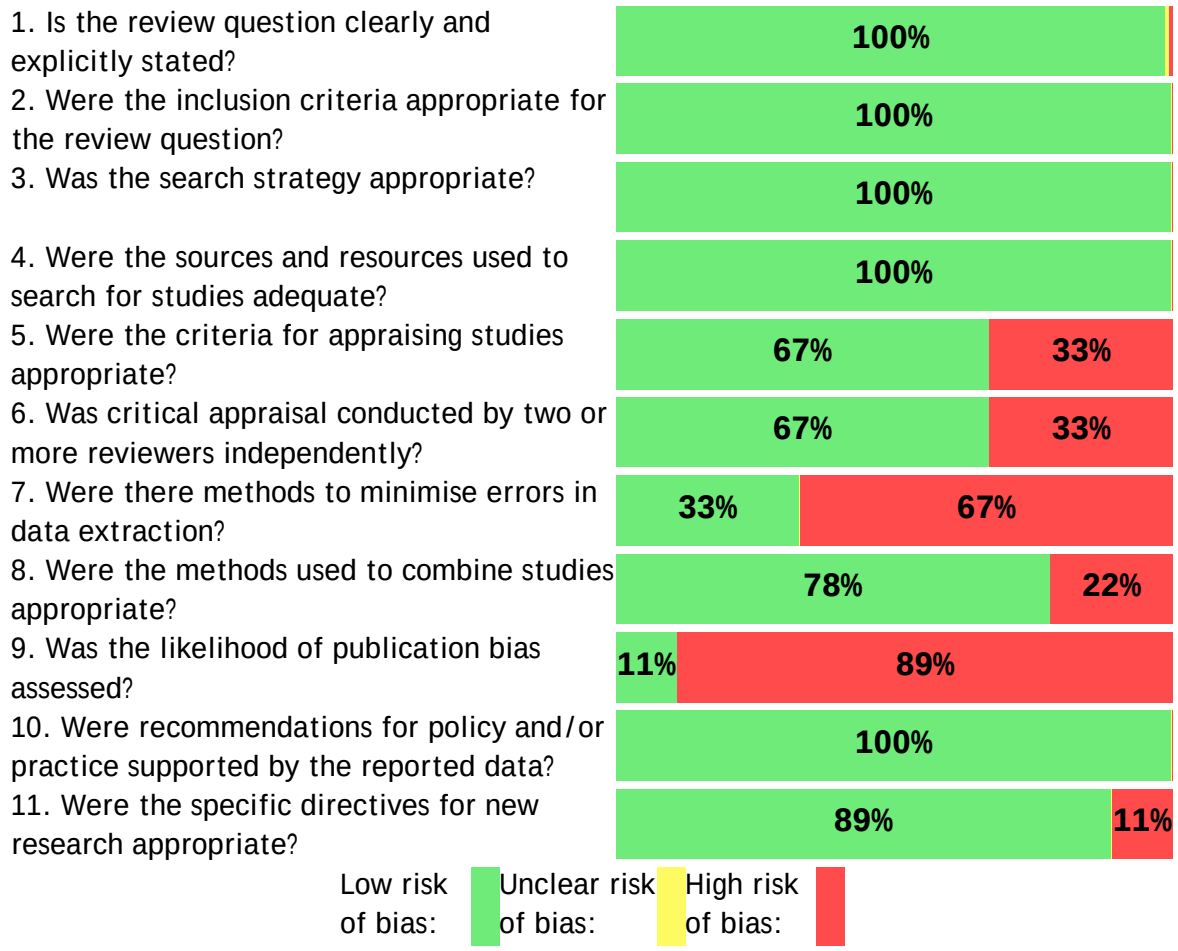
Author, Year **Quality rating (QR)** **Aims**	**Review characteristics**	**Themes**
challenges with traditional warfarin therapy	**Quality assessment of primary studies:** Not reported	apixaban) and timing of doses with respect to meals (dabigatran and rivaroxaban) are all additional factors that might make it difficult for some patients to accept, manage and adhere to the NOACs. Forgetfulness, attitudes toward stroke and bleeding risk, condition-related factors, social and economic factors, and healthcare system-related factors, will likely influence patients' adherence to NOACs in a manner similar to warfarin.
Wilke et al. (2017) **QR** 9/11 **Aims** to conduct a systematic literature review summarising the results of studies dealing with the preferences of AF patients towards OAC treatment.	**Population:** Patients with AF **Drug(s):** Warfarin and NOACs **Number of included primary studies:** N=27 included studies; 16 OACs in general, 11 NOACs vs. warfarin; 7,295 patient and 266 physicians **Type of included primary studies:** **-** quantitative studies of patients preferences **Quality assessment of primary studies:** reported but no previously developed tool described	**Preferences and Choices** ***Patients*** All the publications analysed reported a high variability of AF patient preferences towards anticoagulation treatment; some of the analyses even identified specific AF patient segments, defined by different degrees of bleeding risk aversion. Data show that AF patients, in accordance with clinical guidelines, weigh clinical attributes such as stroke or bleeding risk more heavily than convenience attributes. Therefore, it is in line with the preferences of AF patients that a treating physician first investigates the clinical effectiveness and safety of the recommended anticoagulant before suggesting alternative treatment choices to the patient. Most studies showed that patients were willing to accept higher bleeding risks if a certain threshold in stroke risk reduction could be reached. Preferences of AF patients towards OACs may differ from the perspective of clinical guidelines or the perspective of physicians. This review also showed that if alternative OAC treatments are similar in terms of efficacy and safety, as is the case with may

Author, Year Quality rating (QR) Aims	Review characteristics	Themes
		AC options in AF, convenience attributes such as mode of application, interactions with food or drugs, availability of an antidote, need for bridging, or frequency of application may matter to patients. It has been shown that a less frequent dosing schedule, such as once daily on chronic cardiovascular disease medication, is associated with higher treatment adherence.
Willett and Morrill (2017) **QR** 5/11 **Aims** to describe current recommended dosing for each NOAC and published post-marketing data, including case reports, on the use of these agents in the renally impaired; and discuss patient adherence and satisfaction and the cost of these agents	**Population:** Patients with reduced renal function **Condition:** AF and VTE **Drug(s):** NOACs: Dabigatran Rivaroxaban Apixaban **Number of included primary studies:** N=unclear; findings from 9 studies cited but authors report pulling findings from ten studies **Type of included primary studies:** **-** Systematic review - Meta-analyses - Trial - Surveys	**Perceptions and Attitudes** ***Patients*** Most of the studies have focused on patients' willingness to switch from warfarin to dabigatran or their satisfaction with dabigatran. Frequency of blood tests, along with dosing frequency and drug–food interactions, were considered less important than efficacy and safety. Likewise, cost was of high importance, and the affinity for newer agents increased as cost decreased. Further, data from patient-adherence studies have suggested that NOACs that are dosed daily (rather than twice daily) are optimal and preferred.

Author, Year **Quality rating (QR)** **Aims**	**Review characteristics**	**Themes**
	Quality assessment of primary studies: Not reported	
Zhou et al. (2016) **QR** 10/11 **Aims** to compare the effectiveness of pharmacist-managed anticoagulation control of warfarin with other models	**Population:** Patients on warfarin therapy **Condition:** Majority AF and VTE; some focused on additional conditions **Drug(s):** Warfarin **Number of included primary studies:** N=8 included studies; 1,493 participants **Type of included primary studies:** **-** RCTs **Quality assessment of primary studies:** Cochrane risk of bias tool	**Behaviour and Uptake** ***Patients*** The pharmacist-led AM group showed a significantly higher patients' satisfaction score compared with that of the other managed groups, which has been attributed to an improved satisfaction in the quality of patient life (i.e. self-efficacy, strained social network, daily hassles, and distress), pharmacist service, interpersonal manner, communication, time spent and accessibility. The outcome of percentage of time within the therapeutic range in this study indicated that pharmacists provided significantly better AC control of warfarin in the standard therapeutic range, but not in the expanded therapeutic range. In the pharmacist-led INR group, the INR was controlled more strictly and adjusted more cautiously. In the RCTs, pharmacists played a key role in warfarin anticoagulation treatment to achieve better anticoagulation control and patients' satisfaction. The pharmacists focused more effort on clinical counselling, patient education, home visit monitoring, anticoagulation clinical, standardised follow-up and comprehensive pharmaceutical care.

Appendix 27: Reviews of stakeholder experiences; risk of bias assessment of included reviews

First author (year)	1. Is the review question clearly and explicitly stated?	2. Were the inclusion criteria appropriate for the review question?	3. Was the search strategy appropriate?	4. Were the sources and resources used to search for studies adequate?	5. Were the criteria for appraising studies appropriate?	6. Was critical appraisal conducted by two or more reviewers independently?	7. Were there methods to minimise errors in data extraction?	8. Were the methods used to combine studies appropriate?	9. Was the likelihood of publication bias assessed?	10. Were recommendations for policy and/or practice supported by the reported data?	11. Were the specific directives for new research appropriate?
Alamneh (2016)	+	+	+	+	-	-	-	-	-	+	+
Clarkesmith (2017)	+	+	+	+	+	+	+	+	-	+	+
Entezari-Maleki (2016)	+	+	+	+	+	+	-	+	-	+	+
Loewen (2017)	+	+	+	+	+	+	+	+	-	+	+
Mas Dalmau (2017)	+	+	+	+	+	+	+	+	-	+	+
Pandya (2017)	+	+	+	+	-	-	-	+	-	+	+
Wilke (2017)	+	+	+	+	+	+	-	+	-	+	+
Willett (2017)	+	+	+	+	-	-	-	-	-	+	-
Zhou (2016)	+	+	+	+	+	+	-	+	+	+	+


1. Is the review question clearly and explicitly stated?
100%
2. Were the inclusion criteria appropriate for the review question?
100%
3. Was the search strategy appropriate?
100%
4. Were the sources and resources used to search for studies adequate?
100%
5. Were the criteria for appraising studies appropriate?
67%
33%
6. Was critical appraisal conducted by two or more reviewers independently?
67%
33%
7. Were there methods to minimise errors in data extraction?
33%
67%
8. Were the methods used to combine studies appropriate?
78%
22%
9. Was the likelihood of publication bias assessed?
11%
89%
10. Were recommendations for policy and/or practice supported by the reported data?
100%
11. Were the specific directives for new research appropriate?
89%
11%
Low risk of bias:
Unclear risk of bias:
High risk of bias:

Appendix 28: Reviews of stakeholder experiences; overlap of included primary studies

Review / Included Studies	Alamneh (2016)	Clarkesmith (2017)	Entezari-Maleki (2016)	Loewen (2017)	Mas Dalmau (2017)	Pandya & Bajorek (2017)	Wilke (2017)	Willett & Morrill (2017)	Zhou (2016)	Overlap
Akao (2014)	✓									
Alonso-Coello (2014)				✓			✓			2
Anderson (2006)					✓					
Andrade (2016)				✓			✓			2
Ansell (2010)						✓				
Arnsten (1997)						✓				
Attaya (2012)				✓		✓	✓	✓		4
Bajorek (2007)					✓	✓				2
Bajorek (2009)						✓				
Baker (2009)	✓									
Bannerjee (2012)	✓									
Barcellona (2000)						✓				
Barcellona (2015)							✓			
Barnes (2014)	✓									
Beyth (2000)		✓								
Biskupiak (2014)	✓									
Boom (2015)							✓			
Bottger (2015)				✓			✓			2
Brandes (2013)	✓									
Bungard (2009)			✓							
Bungard (2012)			✓							
Camm (2010)	✓									

Review / Included Studies	Alamneh (2016)	Clarkesmith (2017)	Entezari-Maleki (2016)	Loewen (2017)	Mas Dalmau (2017)	Pandya & Bajorek (2017)	Wilke (2017)	Willett & Morrill (2017)	Zhou (2016)	Overlap
Camm (2016)								✓		
Casais (2005)						✓	✓			2
Chamberlain (2001)			✓							
Chan (2006)									✓	
Chan (2011)	✓									
Choi (2014)				✓		✓				2
Christensen (2007)		✓								
Clarkesmith (2013)		✓								
Coelho-Dantas (2004)					✓					
Coleman (2004)			✓							
Coleman (2013)								✓		
Cottrell (2009)							✓			
Cutler & Everett (2010)	✓									
Dantas (2004)						✓				
Davis (2005)						✓				
De Caterina (2013)	✓									
De Schryver (2005)	✓									
Decker (2012)					✓					
Deitelzweig (2012)	✓									
Deitelzweig (2013)	✓									
Deitelzweig (2014)	✓									
Desai (2013)	✓									
Desai (2014)	✓									

Review **Included Studies**	Alamneh (2016)	Clarkesmith (2017)	Entezari-Maleki (2016)	Loewen (2017)	Mas Dalmau (2017)	Pandya & Bajorek (2017)	Wilke (2017)	Willett & Morrill (2017)	Zhou (2016)	Overlap
Devereaux (2001)				✓			✓			2
DeWilde (2006)	✓									
Duran (2012)	✓									
Duran-Parrondo (2011)			✓							
Eikelboom (2013)	✓									
Elewa (2014				✓		✓		✓		3
Ernst (2003)			✓							
Fang (2010)	✓									
Fatima (2016)				✓						
Freeman (2011)	✓									
Fuller (2004)					✓	✓				2
Gadisseur (2003)		✓								
Gage (1996)				✓						
Garton (2011)			✓							
Garwood (2008)			✓							
Gebler-Hughes (2012)						✓				
Gebler-Hughes (2014)							✓			
Ghijben (2014)				✓			✓	✓		3
Gibbs (2013)	✓									
Gonzales-Rojas (2012)							✓			
Greinacher (2015)	✓									
Gupta (2013)			✓							

Review / Included Studies	Alamneh (2016)	Clarkesmith (2017)	Entezari-Maleki (2016)	Loewen (2017)	Mas Dalmau (2017)	Pandya & Bajorek (2017)	Wilke (2017)	Willett & Morrill (2017)	Zhou (2016)	Overlap
Haim (2015)	✓									
Hall (2011)			✓							
Hamilton (2012)	✓									
Hendriks (2013)		✓								
Hodden (2000)			✓							
Holbrook (2007)				✓						
Holbrook (2013)				✓						
Hong (2013)				✓						
Howitt & Armstrong (1999)				✓	✓					2
Howitt (2000)						✓				
Huisman (2015)	✓									
Jackson (2004)			✓							
Kaariainen (2013)						✓				
Kakkar (2011)	✓									
Kim (2011)						✓				
Kimmel (2007)	✓					✓				2
Kirley (2012)	✓									
LaHay (2014)				✓			✓			2
Lalonde (2008)			✓						✓	2
Lancaster (1991)					✓					
Levitan (2013)							✓			
Lip (2002)						✓				
Lip (2006)						✓				

Review **Included Studies**	Alamneh (2016)	Clarkesmith (2017)	Entezari-Maleki (2016)	Loewen (2017)	Mas Dalmau (2017)	Pandya & Bajorek (2017)	Wilke (2017)	Willett & Morrill (2017)	Zhou (2016)	Overlap
Lip (2014)	✓									
Lip (2015)	✓									
Lipman (2004)					✓					
Man-Son-Hing (1996)				✓			✓			2
Man-Son-Hing (1999)		✓		✓						2
Man-Son-Hing (2002)				✓						
McAlister (2005)		✓								
McCormick (2001)	✓									
Mega (2012)	✓									
Michel (2013)						✓				
Mohammed (2013)	✓									
Moia (2013)						✓				
Monz (2013)								✓		
Motycka (2012)			✓							
Najafzadeh (2014)							✓			
Najafzadeh (2015)							✓			
Nelson (2014)						✓				
Nieuwlaat (2006)	✓									
Ogilvie (2010)	✓									
Okumura (2012)							✓			
Okumura (2015)				✓			✓			2
Oldgren (2014)	✓									
Orensky & Holdford (2005)						✓				

Review / Included Studies	Alamneh (2016)	Clarkesmith (2017)	Entezari-Maleki (2016)	Loewen (2017)	Mas Dalmau (2017)	Pandya & Bajorek (2017)	Wilke (2017)	Willett & Morrill (2017)	Zhou (2016)	Overlap
Palacio (2015)				✓			✓			2
Parker (2007)						✓				
Patel-Naik (2008)			✓							
Piyaskulkaew (2014)	✓									
Platt (2008)						✓				
Poon (2007)			✓							
Protherhoe (2000)				✓			✓			2
Prothero (2001)							✓			
Radley (1995)			✓							
Reynolds (2006)	✓									
Robinson (2001)				✓			✓			2
Rudd (2010)			✓							
Shafrin (2016)				✓						
Shah & Gage (2011)	✓									
Shah (2014)	✓									
Sola (2009)					✓					
Sorea (2014)	✓									
Steinberg (2013)	✓									
Suarez (2012)	✓									
Sudlow (1998)				✓						
Sudlow (1999)							✓			
Suryanarayan & Shulman (2014)	✓									
Tan (2012)						✓				

Review **Included Studies**	Alamneh (2016)	Clarkesmith (2017)	Entezari-Maleki (2016)	Loewen (2017)	Mas Dalmau (2017)	Pandya & Bajorek (2017)	Wilke (2017)	Willett & Morrill (2017)	Zhou (2016)	Overlap
Thomson (2007)		✓								
Thorne (2014)						✓	✓			2
Vaughan Sarrazin (2014)						✓				
Verdino (2015)	✓									
Verret (2012)									✓	
Vormfelde (2014)		✓								
Waldo (2005)	✓									
Wang (2013)							✓	✓		2
Wang (2014)	✓									
Wang (2015)							✓			
Waterman (2004)						✓				
Wild (2004)					✓					
Wild (2009)				✓		✓				2
Wilson (2003)			✓							
Wilson (2004)			✓							
Wilt (1995)			✓							
Witt (2003)			✓							
Witt (2005)			✓							
Witt (2013)						✓				
Xu (2013)	✓									
Young (2011)			✓							
Zamorano (2012)						✓	✓			2
Zimetbaum (2010)	✓									

Appendix 29: PRISMA checklist

Section/topic	#	Checklist item	Reported on page number
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Cover page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract 11, Executive summary 12
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	19
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	21
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	11, 18
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	22
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	22
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	92
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	22, 26, 101
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	23, 24
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	23

Risk of bias in individual systematic reviews	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	24
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	24
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	24

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- Undertaking policy-relevant systematic reviews of health and social care research
- Developing capacity for undertaking and using reviews
- Producing new and improved methods for undertaking reviews
- Promoting global awareness and use of systematic reviews in decision-making

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Social Science Research Unit
UCL Institute of Education, University College London
18 Woburn Square
London WC1H 0NR

Tel: +44 (0)20 7612 6397

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telephone: +44 (0)20 7947 9556 email: info@ioe.ac.uk