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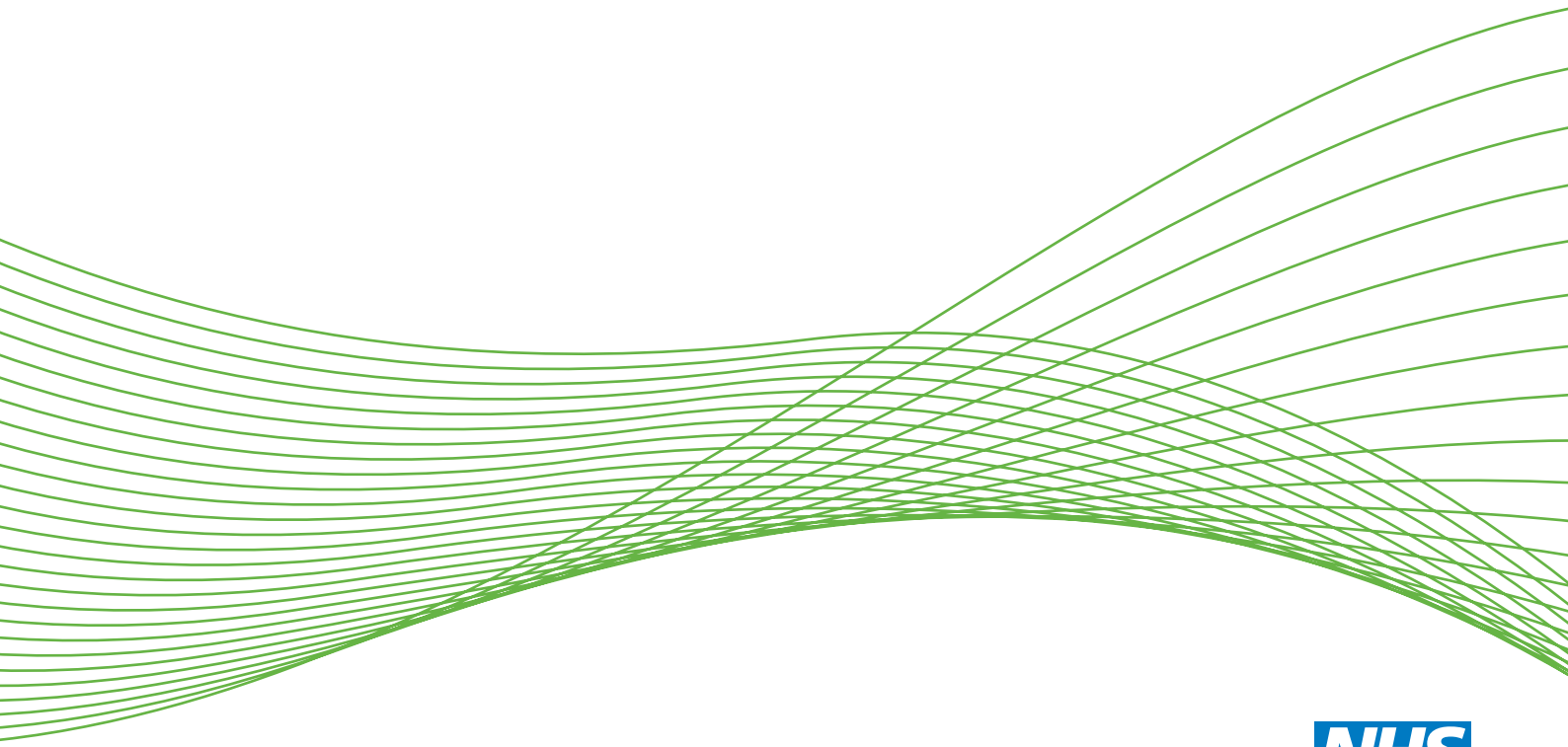

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DA Lane,[1]* S Raichand,[2] D Moore,[2]
M Connock,[2] A Fry-Smith[2] and DA Fitzmaurice[3]
on behalf of the Steering Committee

[1]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK
[2]Public Health, Epidemiology and Biostatistics, University of Birmingham, Birmingham, UK
[3]Primary Care and General Practice, University of Birmingham, Birmingham, UK

*Corresponding author

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Abstract

Combined anticoagulation and antiplatelet therapy for high-risk patients with atrial fibrillation: a systematic review

DA Lane,[1]* S Raichand,[2] D Moore,[2] M Connock,[2] A Fry-Smith[2] and DA Fitzmaurice[3] on behalf of the Steering Committee

[1]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK
[2]Public Health, Epidemiology and Biostatistics, University of Birmingham, Birmingham, UK
[3]Primary Care and General Practice, University of Birmingham, Birmingham, UK

*Corresponding author

Background: Previous research suggests uncertainty whether or not there is any additional benefit in adding antiplatelet therapy (APT) to anticoagulation therapy (ACT) in patients with high-risk atrial fibrillation (AF) in terms of reduction in vascular events, including stroke. The existing guidelines acknowledge an increased risk of bleeding associated with such a strategy; however, there is no consensus on the treatment pathway.

Objectives: To determine, by undertaking a systematic review, if the addition of APT to ACT is beneficial compared with ACT alone in patients with AF who are considered to be at high risk of thromboembolic events (TEs).

Data sources: Data sources included bibliographic databases {the Cochrane Library [Cochrane Central Register of Controlled Trials (CENTRAL)], MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, ClinicalTrials.gov, National Institute for Health Research (NIHR) Clinical Research Network Portfolio, Current Controlled Trials (CCT) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)}, reference lists from identified systematic reviews and relevant studies, and contact with clinical experts. Searches were from inception to September 2010 and did not use language restrictions or study design filters.

Review methods: Studies of any design were included to evaluate clinical effectiveness, including randomised controlled trials (RCTs), non-randomised comparisons, cohort studies, case series or registries, longitudinal studies, systematic reviews and meta-analyses, and conference abstracts published after 2008. Inclusion criteria consisted of a population with AF, at high-risk of TEs, aged ≥18 years, on combined ACT and APT compared with others on ACT alone or ACT plus placebo. Inclusion decisions, assessment of study quality and data extraction were undertaken using methods to minimise bias.

Results: Fifty-three publications were included, reporting five RCTs (11 publications), 18 non-randomised comparisons (24 publications) and 18 publications that reported reviews, which added no further data. There was variation in the population, types and doses of ACT and APT, definitions of outcomes, and length of follow-up between the studies. There was a paucity of directly randomised high-quality RCTs, whereas non-randomised comparisons were found to have significant confounding factors. No studies looked at the effect of ACT plus APT compared with ACT alone on vascular events in patients with AF following acute coronary syndrome (ACS) or percutaneous coronary intervention. In most studies,

significant differences in event rates were not seen between the patients on combined therapy compared with those on ACT alone for outcomes such as stroke (including haemorrhagic and ischaemic strokes), rates of transient ischaemic attacks, composite end points of stroke and systemic embolism (SE), SE alone, acute myocardial infarction, mortality (vascular or all cause) or bleeding events. There was conflicting evidence regarding rates of major adverse events consisting of composite end points, although event rates were generally low.

Limitations: An attempt was made to identify all of the available evidence around the subject despite the dearth of directly randomised studies using a robust review methodology. There was a paucity of directly randomised evidence to undertake a meta-analysis for the merits of one technology over another. The selection criteria were kept necessarily broad with regard to the population, intervention and comparator in order to capture all relevant studies.

Conclusions: This systematic review suggests that there is still insufficient evidence to advocate a clear benefit of the addition of APT to ACT compared with ACT alone in reducing the risk of vascular events in a population of patients at high risk of TEs resulting from AF. It is recommended that a definitive prospective RCT needs to be undertaken in a population at high risk of atherosclerotic coronary artery and other vascular events in addition to being at high risk of AF-mediated TEs. From the UK context, at the time of writing, any future trial should compare adjusted-dose warfarin [international normalised ratio (INR) 2.0–3.0] plus aspirin (75–325 mg) with adjusted-dose warfarin (INR 2.0–3.0). However, given the emergence of newer anticoagulation agents (dabigatran, rivaroxaban and apixaban) this prioritisation may need to be revisited in the future to reflect current best clinical practice.

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Contents

Glossary

Acute coronary syndrome Acute coronary artery disease, including unstable angina and non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction.

Antiplatelet agent Type of anticlotting agent that works by inhibiting blood platelets. Antiplatelet drugs include clopidogrel, dipyridamole and aspirin.

Aspirin A salicylate drug inhibitor of platelet aggregation.

Cerebrovascular Pertaining to the blood vessels of the brain.

Clopidogrel A thienopyridine – an inhibitor of platelet aggregation.

Coronary arteries The arteries that supply the heart muscle with blood.

Coronary artery disease Gradual blockage of the coronary arteries, usually by atherosclerosis.

Coronary heart disease Narrowing or blockage of the coronary arteries of the heart by atheroma; often leads to angina, coronary thrombosis or heart attack, heart failure and/or sudden death.

Dipyridamole Inhibitor of platelet aggregation, also available in combination with aspirin.

Electrocardiogram A recording of the electrical signals from the heart.

Haemorrhagic stroke Death of brain cells because of bleeding in the brain.

Heterogeneity Variability among studies, which could be clinical, methodological or statistical.

Infarction Death of tissue following interruption of the blood supply.

Intention-to-treat analysis A method of data analysis in which all patients are analysed in the group to which they were assigned at randomisation, regardless of any variation to this.

International normalised ratio A measure for reporting the results of blood coagulation (clotting) tests for individuals on vitamin K antagonists.

Ischaemia A low oxygen state, usually due to obstruction of the arterial blood supply or inadequate blood flow leading to hypoxia in the tissue.

Ischaemic stroke Death of brain cells caused by blockage in a cerebral blood vessel.

Meta-analysis A quantitative method for synthesising data by combining similar outcomes of many similar studies.

Myocardial infarction Damage to the heart muscle caused by obstruction of circulation to a region of the heart. Also called a heart attack.

Non-ST-segment elevation myocardial infarction A myocardial infarction that is not associated with elevation of the ST segment on an electrocardiogram.

Occlusive vascular event An event caused by the blockage of an artery, due to myocardial infarction, unstable angina, ischaemic stroke, transient ischaemic attack or peripheral arterial disease.

Peripheral arterial disease A condition in which the arteries that carry blood to the arms or legs become narrowed or clogged, slowing or stopping the flow of blood. Also known as peripheral vascular disease.

Plaque Atheromatous plaque is a swelling on the inner surface of an artery produced by lipid deposition.

Relative risk The proportion of people experiencing the event of interest among those exposed to the relevant (risk) factor (e.g. drug) divided by the proportion of people experiencing the event of interest among those not exposed to the risk factor.

ST-segment elevation myocardial infarction A myocardial infarction associated with elevation of the ST segment on the electrocardiogram.

Stroke The sudden death of brain cells because of a lack of oxygen when blood flow to the brain is impaired by a blockage or rupture of an artery to the brain, causing neurological dysfunction.

Thrombus An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements; frequently causes vascular obstruction at the point of its formation.

Transient ischaemic attack A brain disorder caused by temporary disturbance of blood supply to an area of the brain, resulting in a sudden, brief (< 24 hours, usually < 1 hour) decrease in brain function.

Unstable angina Angina pectoris (chest pain) in which the cardiac pain has changed in pattern or occurs at rest.

Vascular disease Any disease of the circulatory system.

List of abbreviations

ACC	American College of Cardiology
ACS	acute coronary syndrome
ACT	anticoagulant therapy
AF	atrial fibrillation
AFASAK II	Second Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation Study
AHA	American Heart Association
AMI	acute myocardial infarction
APT	antiplatelet therapy
ATT	antithrombotic therapy
CAD	coronary artery disease
$CHADS_2$	Congestive heart failure, Hypertension, Age $\geq$ 75 years, Diabetes mellitus, and prior Stroke or TIA or thromboembolism
CI	confidence interval
CRD	Centre for Reviews and Dissemination
ESC	European Society of Cardiology
FFAACS	Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontané study
GI	gastrointestinal
HF	heart failure
HTA	Health Technology Assessment
ICH	intracranial haemorrhage
INR	international normalised ratio
IPD	individual participant data
ITT	intention to treat
LV	left ventricle/ventricular
LVEF	left ventricular ejection fraction
MI	myocardial infarction
NASPEAF	NAtional Study for Prevention of Embolism in Atrial Fibrillation
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OAC	oral anticoagulant
ODTI	oral direct thrombin inhibitors
PCI	percutaneous coronary intervention
PETRO	dabigatran with or without concomitant aspirin compared with warfarin alone in patients with non-valvular atrial fibrillation study
RCT	randomised controlled trial
RR	relative risk
SE	systemic embolism
SPAF III	Stroke Prevention in Atrial Fibrillation III study
SPORTIF	Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation study

TE	thromboembolism/ thromboembolic event	TTR	time in therapeutic range
TIA	transient ischaemic attack	VKA	vitamin K antagonist

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Scientific summary

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and is a major risk factor for stroke. The main risk factors for stroke among patients with AF include previous stroke or transient ischaemic attack (TIA), age ≥75 years, heart failure (HF), hypertension and diabetes mellitus, which constitute the recommended and widely used stroke risk assessment tool, the $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, and prior Stroke or TIA or thromboembolism) score. There is evidence that thromboprophylaxis with warfarin reduces the risk of thromboembolism (TE) compared with placebo or aspirin, whereas aspirin reduces the risk of thromboembolism in patients with AF compared with placebo. However, it is currently unclear whether or not there is any additional benefit in adding antiplatelet therapy (APT) to anticoagulation therapy (ACT) in patients who are at high risk of thromboembolic events (TEs) resulting from AF in terms of a reduction in vascular events, including stroke. The existing guidelines acknowledge an increased risk of bleeding associated with such a strategy; however, there is no consensus on the treatment pathway.

Objectives

To determine, by undertaking a systematic review, if the addition of APT to ACT is beneficial compared with ACT alone in patients with AF who are considered to be at a high risk of TEs.

Methods

Data sources including bibliographic databases (e.g. The Cochrane Library, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations and EMBASE), reference lists from identified systematic reviews and relevant studies, and contact with clinical experts were used. Searches were from inception to September 2010 and did not use language restrictions or study design filters. Study selection process was undertaken in three stages on criteria decided a priori by two reviewers independently. Both randomised and non-randomised studies that reported data for patients on a combination of any anticoagulant plus any APT, as well as those on ACT alone, were included. Systematic reviews and meta-analyses that met the inclusion criteria were utilised to identify further articles. Data were extracted from the main and supporting publications (where relevant) of all included primary studies by one reviewer and checked by a second reviewer. Disagreements were resolved by consensus or by referral to a third reviewer. The methodological quality of the included studies was assessed. Pooling of results was not attempted for the assessment of effectiveness of individual technologies because of the substantial clinical and methodological heterogeneity between studies.

Results of the literature review

Fifty-three publications were included in the review. Of these, five were randomised controlled trials (RCTs) (11 publications), 18 (24 publications) reported non-randomised comparisons for the therapies of interest, and 18 publications were systematic reviews. Three RCTs and 14 other studies reporting non-randomised comparisons summarised data for warfarin plus an antiplatelet agent compared with warfarin. One RCT and one non-randomised study reported data on acenocoumarol (Sinthrome®, Alliance) plus an APT compared with acenocoumarol alone. The remaining one RCT reported data on fluindione plus aspirin compared with fluindione plus placebo. One study reporting non-randomised comparisons used

idraparinux, and one used dabigatran (Pradaxa®, Boehringer Ingelheim) as an anticoagulant agent, while two studies reported data on ximelagatran plus warfarin compared with ximelagatran alone. Doses of ACT and APT varied between studies. The included studies were not found to be of high quality. The studies reporting non-randomised comparisons were found to have significant confounding factors. There was paucity of directly randomised high-quality RCTs comparing ACT plus APT in recommended doses with ACT alone in a high-risk population. For this reason, non-randomised studies were sought. No studies compared the effect of ACT plus APT with ACT alone on vascular events in patients with AF following acute coronary syndromes or percutaneous coronary intervention.

Summary of benefits and harms

The primary outcome measures assessed in this review were stroke, TIA, systemic embolism (SE), composite end point of SE and stroke, myocardial infarction, vascular death and secondary outcome measures of all-cause mortality and bleeding events based on separate consideration of the individual studies; no meta-analyses were undertaken. Outcomes definitions varied between the studies.

The majority of the included studies did not report a significant difference in event rates between the patients on combined therapy and those on ACT alone. There was conflicting evidence regarding the benefit of combination therapy over anticoagulation alone in the reduction of all stroke events, with no RCT demonstrating a significant difference between the study arms and poor-quality non-randomised data reporting more events with the combination therapy. Very few studies reported haemorrhagic and ischaemic strokes separately. Of those that reported haemorrhagic strokes, the event rates were small and there was no evidence of an increased risk of haemorrhagic strokes on either combined therapy or ACT alone. Furthermore, there was conflicting evidence regarding the reduction of ischaemic stroke, with only one study demonstrating a significant increase in risk in patients on combination therapy. Very few TIA events were reported, with no significant benefit of either therapy in reducing the risk. No clear evidence was available for benefit of either therapy in the reduction of the combined end point of stroke and SE, with one RCT suggesting a significant increased risk with the combination therapy, and one larger non-randomised comparison reporting similar rates in both groups. No evidence was found to clearly signify a benefit of combined ACT plus APT or ACT alone for either SE or acute myocardial infarction (AMI). No evidence was found to suggest that combination therapy significantly reduced the risk of mortality (vascular or all-cause) compared with ACT alone. There was no clear consensus between studies for the risk of bleeding events. Combination therapy was observed to increase the risk of bleeding compared with ACT alone in one small RCT, whereas one large non-randomised study reported similar levels of bleeding in both groups. Rates of major adverse events consisting of composite end points were lower with combination therapy for the composite end points of severe bleeding, non-fatal stroke, TIA, SE and vascular death and also for non-fatal stroke, TIA, SE and vascular death, whereas, in one study, combination therapy conferred a significantly increased risk of the composite end point of stroke, SE and vascular death compared with ACT alone.

Therefore, there appears to be insufficient evidence to suggest a clear benefit of the addition of APT to ACT compared with ACT alone in reducing the risk of vascular events in an AF population at high risk of TEs.

Discussion

The review included 23 primary studies, not all of which were necessarily of good quality. No study reported a robust, randomised comparison in a high-risk AF population of combined ACT targeting an international normalised ratio (INR) of 2.0–3.0 plus additional APT and ACT alone (target INR 2.0–3.0), which was considered the ideal study in the current context.

The five included RCTs investigated different doses of anticoagulant plus antiplatelet or anticoagulant alone in patients at variable (or unspecified) stroke risks. The type and dosage of both ACT and APT also differed in the studies.

The quality of the 18 studies that reported non-randomised comparisons was generally poor. The sample size and follow-up times in these studies varied greatly. Of note is the confounding of study results by indication for APT in these studies, which was used at physicians' discretion in most studies or clearly indicated for cardiovascular diseases in a few others. The time of antiplatelet administration also varied between the studies. Most studies were retrospective in nature, with patient data being identified from a register of records, with some information on various study quality features missing or unclear.

The population varied greatly between all included studies. None of the included studies reported data for a specified high-risk population with a $CHADS_2$ [congestive HF, hypertension, age ≥75 years, diabetes mellitus (1 point for each risk factor), stroke/TIA (2 points)] score of ≥2. The majority of non-randomised comparisons did not specify the stroke risk of the sample. Almost all non-randomised studies were conducted on hospital patients. Only two of the five included randomised studies investigated ACT with the recommended target INR range of 2.0–3.0 in both study arms. Data from many of the non-randomised comparisons did not add further information to the RCT data.

The heterogeneity between the studies warranted a narrative review and numerical pooling of study data was not possible.

Strengths and limitations

An attempt was made to identify all the available evidence around the subject despite the dearth of directly randomised studies using a robust review methodology. There was a paucity of directly randomised evidence to undertake a meta-analysis of the merits of one technology over another. The selection criteria were kept necessarily broad with regard to the population, intervention and comparator in order to capture all relevant studies.

Conclusions

There are not sufficient data from the five randomised comparisons and 18 non-randomised comparisons to conclude whether or not there are patients with AF who would benefit from combined ACT and APT compared with ACT alone.

Suggested research

It is recommended that a definitive prospective RCT needs to be undertaken with a sufficient duration of follow-up, preferably in a population at high risk of atherosclerotic coronary artery and other vascular events in addition to being at high risk of AF-mediated TEs. Any such trial should consider the issues of the population, which would need to be clearly defined taking into account the different risk stratification scores which would allow clinicians and policy-makers to interpret the findings. The intervention(s) would need to be clearly defined. The study would need to address the potential class effects of both anticoagulant and antiplatelet agents and should use standard current therapy. The comparator group should receive the same ACT as the intervention group with similarly achieved INRs reported for both groups. From the UK context, at the time of writing, any future trial should compare adjusted-dose warfarin (INR 2.0–3.0) plus aspirin (75–325 mg) with adjusted-dose warfarin (INR 2.0–3.0). However, given the emergence of newer anticoagulation agents [dabigatran, rivaroxaban (Xarelto®, Bayer) and apixaban

(Eliquis®, Bristol-Myers Squibb)] this prioritisation may need to be revisited in the future to reflect current best clinical practice. A health economic analysis would add value to findings. All outcomes would need to be clearly defined and validated.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Description of the underlying health problem

Atrial fibrillation (AF), the most common abnormality of the heart's rhythm (cardiac arrhythmia) seen in clinical practice,[1] is characterised by unco-ordinated and rapid beating of the upper chambers of the heart (atria).[2]

Owing to the irregularity in the beating of the heart, the flow of blood is affected and there is an increased risk of formation of blood clots in the atria. If these clots are subsequently displaced, they can travel in the blood to other parts of the body and may block blood vessels, thereby disrupting blood flow, leading to an embolism. The most common site of embolism in patients with AF is the brain, resulting in a stroke. Patients with AF have an increased risk of stroke compared with individuals without AF.[3] AF is responsible for 15% of all strokes and one-quarter of strokes in people aged >80 years.[4] Furthermore, AF confers a 1.5- and 1.9-fold increased risk of mortality in men and women, respectively,[5] and is associated with elevated risk of developing heart failure (HF)[2] and impairment of quality of life.[6,7]

Incidence/prevalence

Atrial fibrillation is the most common cardiac arrhythmia in clinical practice[1,8,9] and the prevalence increases markedly with older age, from 0.5% at 40–50 years to 5% in those aged ≥65 years and almost 10% in people aged ≥80 years.[10,11] AF is slightly more prevalent in men than in women.[8–10] The lifetime risk of developing AF aged ≥40 years is approximately one in four.[8,9]

The Screening for Atrial Fibrillation in the Elderly (SAFE) study,[12] a randomised controlled trial (RCT) of systematic screening (targeted and total population screening) compared with routine practice for the detection of AF in people aged ≥65 years in the UK involving 15,000 patients, revealed that the prevalence of AF was 7.2%, with a higher prevalence evident in men (7.8%) and those aged ≥75 years (10.3%). The incidence of AF ranged from 1.04% to 1.64% per year. The incidence and prevalence of AF are increasing and are projected to rise exponentially as the population ages and the prevalence of cardiovascular risk factors increases.[10]

Impact of the health problem

The major complication of AF is stroke. AF is associated with a fivefold increased risk of stroke compared with age- and sex-matched patients in sinus rhythm,[3] and doubles the risk of stroke after adjustment for other risk factors.[1] In addition, when a stroke occurs in a patient with AF it is more severe, more likely to recur, and more likely to result in death or disability than strokes in patients without AF.[13–15] Further, stroke survivors with AF face persistent neurological deficits and permanent disability, having a significant negative impact on their quality of life and increasing the burden of care for their family and the health services.[16]

Information from The Office of Health Economics[17] demonstrates the huge economic burden of AF to the NHS. In 2008, patients with AF accounted for 5.7 million bed-days, at a cost to the NHS of £1873M. In addition, other inpatient costs accounted for an extra £124M and outpatient costs (such as electrocardiography, monitoring anticoagulant treatment and post-discharge attendance) a further £205M. However, this figure does not take into account the significant societal costs, days of work lost, informal care, and the impact of AF on the patient and his or her family. The cost of AF appears to have

increased dramatically since the turn of the century, given that a previous study estimated that the direct cost of AF to the NHS in 2000 was £45M, equivalent to 0.97% of total NHS expenditure.[18]

Risk of stroke

The risk of stroke among patients with AF is heterogeneous, with risk dependent on associated comorbidities. The Stroke Risk in Atrial Fibrillation Working Group[19] conducted a systematic review to identify independent predictors of stroke in patients with AF and found that a previous stroke or transient ischaemic attack (TIA) was consistently and independently associated with an augmented risk of a subsequent stroke, conferring a 2.5-fold increased risk. Increasing age also independently predicted stroke risk, with a 1.5-fold greater risk with each decade of life. In addition, a history of hypertension or elevated systolic blood pressure (>160 mmHg) and diabetes mellitus doubled the stroke risk. Half of the studies that examined sex as a risk factor for stroke demonstrated that women had a 1.6-fold greater risk than men.[19] A history of HF and coronary artery disease (CAD) were not identified as independent risk factors for stroke by this systematic review, although systolic dysfunction (evidenced by echocardiography) was found to be a risk factor.[19] The risk of stroke in patients with AF is significantly reduced with anticoagulation therapy,[20–23] and antiplatelet treatment also decreases the risk of stroke compared with placebo.[20]

Current service provision

Antithrombotic management of atrial fibrillation

The management of AF consists of a rate and/or rhythm control strategy in combination with antithrombotic therapy (ATT). The aim of the former is to control the heart rate without attempting to restore the heart's normal rhythm (sinus rhythm), whereas the latter attempts to re-establish and maintain sinus rhythm. Regardless of which strategy is implemented, all patients should be assessed for individual stroke risk and receive appropriate ATT. Clinical guidelines[2,24] recommend oral anticoagulant for patients who are at high risk of stroke, and either oral anticoagulation or antiplatelet(s) for those deemed to be at intermediate risk, although the European Society of Cardiology (ESC) guidelines[2] prefer oral anticoagulation over antiplatelet(s) therapy in this group. Among those patients who are at low risk of stroke (those <65 years of age with no stroke risk factors), the National Institute for Health and Care Excellence (NICE)[24] recommends antiplatelet therapy (APT), whereas the ESC guidelines[2] recommend APT or no treatment, with a preference for no therapy.[2,24]

In order to determine the most appropriate ATT for each patient, his or her individual risk of stroke should be assessed. The main risk factors for stroke among patients with AF are described above (see *Risk of stroke*), but include previous stroke or TIA, age ≥65 years, HF, hypertension and diabetes mellitus, which together constitute the widely used stroke risk assessment tool, the $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, and prior Stroke or TIA or thromboembolism) score,[25] although there are numerous other stroke risk stratification schemas available[19] (*Table 1*).

In the UK, the NICE guidelines[24] currently recommend aspirin 75–300 mg daily (unless contraindicated) for patients aged <65 years with no moderate- or high-risk factors and who, thus, are deemed to be at low risk (≤1% annual risk) of stroke. For patients at moderate risk (4% annual risk), namely those aged <75 years with hypertension, diabetes mellitus or vascular disease (CAD or peripheral artery disease) and those ≥65 years without any high-risk factors, NICE[24] suggests anticoagulation or aspirin. Among patients at high risk (12% annual risk) of stroke, i.e. those with a previous stroke/TIA or thromboembolism (TE), clinical evidence of valve disease, HF, or impaired left ventricular (LV) function on echocardiography, or aged ≥75 years with hypertension, diabetes mellitus or vascular disease, NICE[24] recommends anticoagulation with warfarin. The ESC guidelines[2] have adopted a risk factor-based approach to determine appropriate thromboprophylaxis (*Figure 1* and *Table 1*) and these guidelines have superseded the NICE recommendations in clinical practice in the UK.[2]

TABLE 1 Stroke risk stratification schemes in AF

Risk stratification scheme, year	Risk		
	High	Moderate	Low
AFI, 1994[26]	Previous stroke/TIA, hypertension, diabetes mellitus	Aged ≥65 years with no other risk factors	Aged <65 years
SPAF Investigators, 1999[27]	Previous stroke/TIA, women aged >75 years, men aged >75 years with hypertension	Hypertension, diabetes mellitus	No risk factors
$CHADS_2$, 2001 (classic)[28]	Score of 3–6	Score of 1–2	Score of 0
$CHADS_2$, 2001 (revised)[25]	Score of 2–6	Score of 1	Score of 0
Framingham study, 2003[29]	Score of 16–31	Score of 8–15	Score of 0–7
NICE guidelines, 2006[24]	Previous stroke/TIA/TE, aged ≥75 years with hypertension, diabetes mellitus, or vascular disease, clinical evidence of valve disease, HF, of LV dysfunction on echocardiography	Aged <75 years with hypertension, diabetes mellitus, or vascular disease Aged ≥65 years with no high risk factors	Aged <65 years with no moderate- or high-risk factors
ACC/AHA/ESC guidelines, 2006[1]	Previous stroke/TIA/TE, *or*: or ≥2 moderate risk factors: age ≥75 years, hypertension, HF, LVEF ≤35%, diabetes mellitus	Aged ≥75 years, or hypertension, or HF, or LVEF ≤35%, or diabetes mellitus	No risk factors
Eighth ACCP guidelines, 2008[30]	Previous stroke/TIA/TE, *or*: Two or more moderate risk factors: aged ≥75 years, hypertension, moderately or severely impaired LVEF and/or HF, or diabetes mellitus	Aged >75 years, or hypertension, or moderately or severely impaired LVEF and/or HF, or diabetes mellitus	No risk factors
CHA_2DS_2-VASc, 2010[31]	Score of ≥2	Score of 1	No risk factors
ESC guidelines, 2010[2]	Previous stroke/TIA/SE or aged ≥75 years, *or*: Two or more 'clinically relevant non-major' risk factors: HF or LVEF ≤40%, hypertension, diabetes mellitus, vascular disease,[a] aged 65–74 years, female sex	Score of 1	No risk factors

ACC, American College of Cardiology; ACCP, American College of Chest Physicians; AFI, Atrial Fibrillation Investigators; AHA, American Heart Association; $CHADS_2$, congestive HF, hypertension, age ≥75 years, diabetes mellitus (1 point for each risk factor), stroke/TIA (2 points); CHA_2DS_2-VASc: congestive HF, hypertension, age ≥75 years, diabetes mellitus, stroke/TIA/TE; LV, left ventricle/ventricular; LVEF, left ventricular ejection fraction; SE, systemic embolism; SPAF, Stroke Prevention in Atrial Fibrillation.

a Vascular disease [(MI, peripheral vascular disease, aortic plaque), age 65–74 years, sex category (female) (2 points for stroke/TIA/TE and aged ≥75 years, 1 point for presence of other risk factors].

In patients with AF who have no risk factors for stroke, the ESC guidelines[2] recommend either aspirin 75–325 mg daily or no ATT, with a preference for no treatment over aspirin.[2] For those with one 'clinically relevant non-major' risk factor [HF or left ventricular ejection fraction (LVEF) ≤40%, hypertension, diabetes mellitus, vascular disease, age 65–74 years, female sex], the ESC advises that oral anticoagulation or aspirin (75–325 mg) should be administered, with an oral anticoagulant (OAC) preferred over aspirin. Among those patients with one 'major' (previous stroke/TIA/TE or aged ≥75 years) or two or more 'clinically relevant non-major' risk factors, a OAC is recommended. Where a OAC is recommended, this

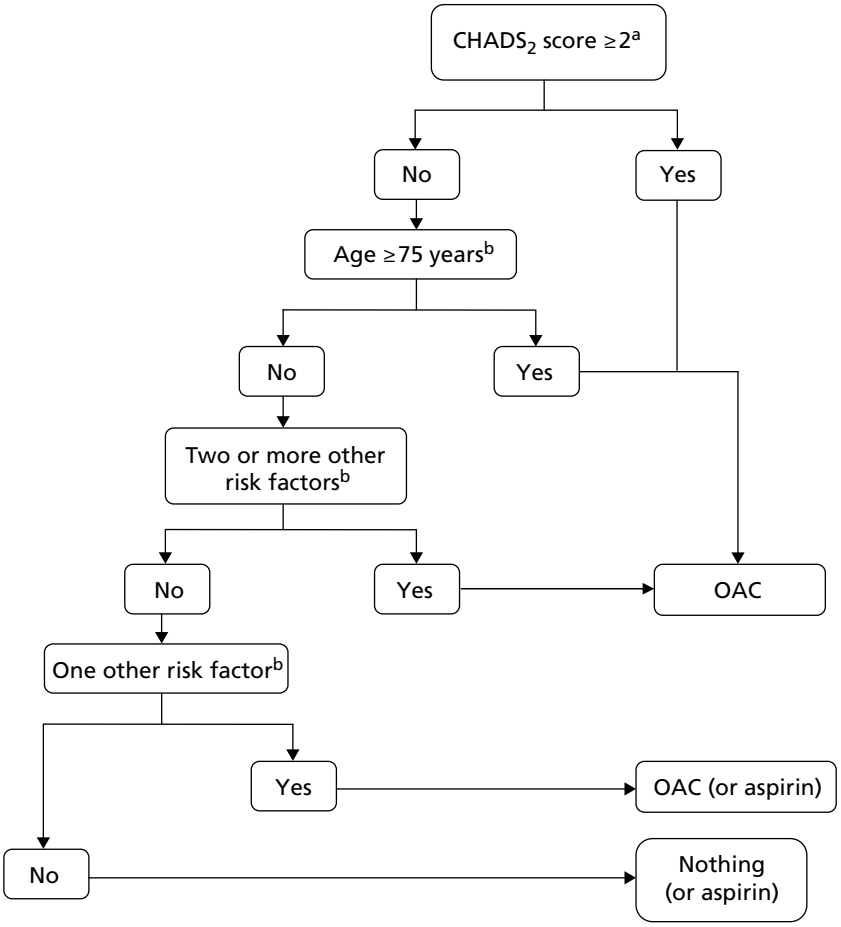

FIGURE 1 Clinical flow chart for the use of ATT in patients with AF. Redrawn from the ESC guidelines.[2] a, Congestive HF, hypertension, age ≥75 years, diabetes mellitus (1 point for each), stroke/TIA/TE (2 points); b, other clinically relevant non-major risk factors: age 65–74 years, female sex, vascular disease.

includes adjusted-dose warfarin (INR 2.0–3.0) or one of the new anticoagulant drugs (see *Description of technology under assessment*).

In addition, CAD is also increasing in prevalence as a consequence of the improvements in survival due to advances in medical therapy and the ageing population.[30] Between 30% and 40% of patients with AF have concomitant CAD,[11] and some of these patients may also require percutaneous coronary intervention (PCI) with stent implantation. Patients with AF and CAD are at increased risk of both stroke and further coronary events. An increasingly common management problem arises when faced with an anticoagulated patient with AF who presents with acute coronary syndrome (ACS) or those who require PCI with stent implantation.[32]

Current guidelines for antithrombotic therapy in atrial fibrillation patients with acute coronary syndrome or undergoing percutaneous coronary intervention or stenting

The joint American College of Cardiology (ACC)/American Heart Association (AHA)/ESC 2006 guidelines on the management of AF recommend that following PCI or revascularisation surgery in patients with AF, low-dose aspirin (<100 mg/day) and/or clopidogrel (75 mg/day) may be given concurrently with anticoagulation to prevent myocardial ischaemic events,[1] although it is acknowledged that these strategies have not been thoroughly evaluated and are associated with an increased risk of bleeding. The 2006 ACC/AHA/ESC guidelines also suggest that clopidogrel should be given for a minimum of 1 month after implantation of a bare-metal stent, ≥3 months for a sirolimus (CYPHER™, Cordis)-eluting coronary stent-P020026,

≥6 months for a paclitaxel (ION™, Boston Scientific)-eluting coronary stent system-P100023, and ≥12 months in selected patients, following which warfarin may be continued as monotherapy in the absence of a subsequent coronary event.[1] Broadly similar recommendations are made in the eighth ACCP guidelines,[33] which suggest that a low dose of aspirin (<100 mg per day) or clopidogrel (75 mg per day) may be given with anticoagulation, although the risk of bleeding may be increased, particularly in elderly patients. The UK NICE guidelines[24] do not address this topic, although acknowledging that adding aspirin to warfarin increases bleeding, and that it is a matter for individual assessment of the risk–benefit ratio in prescribing aspirin plus warfarin in patients with associated CAD.

Furthermore, all of the published guidelines do not address the issue of a presentation with ACS (where PCI is often performed) and bleeding risk. Given the need to balance stroke prevention, recurrent cardiac ischaemia and/or stent thrombosis, two more recent consensus documents,[34,35] based on systematic reviews of patients on OAC undergoing PCI and stenting, advocate initial triple therapy (with OAC, aspirin and clopidogrel) in such patients, and the use of bare-metal stents (owing to the need for prolonged multiple-drug ATT with drug-eluting stents). However, triple ATT is associated with a higher risk of major bleeding and this risk must be considered before treatment initiation.[34,36] Therefore, the ESC Working Group on Thrombosis consensus guidelines[35] recommend limiting triple ATT to 2–4 weeks in patients who are at high risk of haemorrhage (*Table 2*).

TABLE 2 Recommended antithrombotic strategies following coronary artery stenting in patients with AF at moderate to high thromboembolic risk[a]

Haemorrhagic risk	Clinical setting	Stent implanted	Recommendations
Low or intermediate	Elective	Bare metal	• 1 month: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day • Lifelong warfarin (INR 2.0–3.0) alone
	Elective	Drug eluting	• 3 (-olimus group) to 6 (paclitaxel) months: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day • Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day)[b] • Lifelong warfarin (INR 2.0–3.0) alone
	ACS	Bare metal/drug eluting	• 6 months: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day • Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day)[b] • Lifelong warfarin (INR 2.0–3.0) alone
High	Elective	Bare metal[c]	• 2–4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day • Lifelong warfarin (INR 2.0–3.0) alone
	ACS	Bare metal[c]	• 4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day • Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day)[b] • Lifelong warfarin (INR 2.0–3.0) alone

INR, international normalised ratio.

a Redrawn from paper by Lip *et al*., 2010.[35]

b Combination of warfarin (INR 2.0–2.5) + aspirin ≤100 mg/day may be considered as an alternative.

c Drug-eluting stents should be avoided.

Description of technology under assessment

Anticoagulant therapy (ACT) is recommended for patients with AF who are at high risk of stroke. The main type of ACT used for patients with AF is a vitamin K antagonist (VKA), most commonly warfarin, to maintain a therapeutic international normalised ratio (INR) value of 2.0–3.0. Other classes of anticoagulants include heparins (low-molecular-weight heparins), hirudins, and, more recently, the novel anticoagulant drugs, direct oral thrombin inhibitors (ximelagatran and dabigatran), and factor Xa inhibitors [idraparinux, apixaban (Eliquis®, Bristol-Myers Squibb), rivaroxaban (Xarelto®, Bayer) and endoxaban] (*Table 3*). APT is also used for stroke thromboprophylaxis in patients with AF. Antiplatelet agents currently used include aspirin (non-proprietary; typically), clopidogrel (Plavix®, Sanofi-aventis), ticlopidine, dipyridamole (Persantin®, Boehringer Ingelheim) and triflusal (*Table 3*).

Anticoagulation, antiplatelet or combined therapy in high-risk patients with atrial fibrillation

Among patients with AF, there is evidence that thromboprophylaxis with warfarin reduces the risk of TE (by 64%) compared with placebo or aspirin (by 39%).[20] Aspirin reduces the risk of TE in patients with AF by 22% compared with placebo.[20]

However, it is currently unclear whether or not there is any additional benefit in adding APT to ACT in high-risk patients with AF in terms of reduction in vascular events, including stroke.

The available data from individual studies are conflicting, apart from the consistent message that combining APT with oral anticoagulation increases the risk of major bleeding. There is currently no definitive answer to the question of whether or not combination anticoagulant and antiplatelet (mono- and dual-antiplatelet) therapy is beneficial in patients with AF and concomitant CAD/vascular disease, and those undergoing PCI and stent implantation. The available evidence from observational cohort studies

TABLE 3 Types of anticoagulant and antiplatelet agents used for thromboprophylaxis in atrial fibrillation

Anticoagulants	Antiplatelet agents
VKAs • Warfarin sodium • Acenocoumarol (Sinthrome®, Alliance) • Phenindione (non-proprietary) • Fluindione *Heparins* • Low-molecular-weight heparin [bemiparin, dalteparin (Fragmin®, Pfizer), enoxaparin (Clexane®, Sanofi-aventis) and tinzaparin (Innohep®, LEO Pharma)] *Hirudins* • Bivalirudin (Angio®, The Medicines Company) *Direct oral thrombin inhibitors* • Ximelagatran • Dabigatran (Pradaxa®, Boehringer Ingelheim) *Factor Xa inhibitors* • Idraparinux • Apixaban • Rivaroxaban • Endoxaban • Betrixaban • Darexaban	• Aspirin • Clopidogrel • Ticlopidine • Dipyridamole • Triflusal

and registry analyses suggests a reduction in TEs with combination and triple therapy, given for a short duration, in patients with AF and concomitant CAD/vascular disease with stent implantation. However, the risk reduction in TEs is offset by an increased risk of major bleeding.[35]

The aim of the current study is therefore to identify the benefits of adding APT in a subgroup of high-risk patients with AF who are receiving ACT, in whom this can be justified in terms of the balance of reducing vascular events without increasing bleeding.

Chapter 2 Methods

Aim

To determine if the addition of APT to ACT is beneficial compared with ACT alone in patients with AF who are considered to be at high risk of TEs.

Objective

To undertake a systematic review of studies comparing ACT alone with ACT in combination with APT in patients with AF.

Definitions

The *Background* chapter describes AF. For the purposes of this review, the definition of AF used was that determined by the authors of studies.

The *Background* chapter describes ACT and APT used to treat AF. For the purposes of this review, no limits were placed on the type of therapies that could be chosen as being anticoagulant or antiplatelet agents.

High-risk patients of special interest include patients with AF with previous myocardial infarction (MI) or ACS, those undergoing PCI and stent implantation, those with diabetes mellitus, and those with a $CHADS_2$ score of ≥2. However, no restrictions were placed on the determinants of high risk.

Relevant study designs

Given the likely paucity of directly relevant RCTs, the steering group for this project was consulted at an early stage about whether or not evidence from a wider selection of study designs should be reviewed. The steering group decided that this should be the case.

Review methods

Standard systematic review methodology was used, consisting of searches to identify available literature, sifting and the application of specific criteria to identify relevant studies, assessment of the quality of these studies, and the extraction and synthesis of relevant data from them. The review was guided by a protocol that was prepared a priori (see *Appendix 1*) and externally reviewed prior to use.

Search strategies

The following resources were searched for relevant studies:

- Bibliographic databases: The Cochrane Library [Cochrane Central Register of Controlled Trials (CENTRAL)] 2010 Issue 3; MEDLINE (Ovid) 1950 to September week 1 2010; MEDLINE In-Process and Other Non-Indexed Citations from inception to 27 September 2010; and EMBASE (Ovid) 1980 to September 2010. Searches were based on index and text words that encompassed the population: atrial fibrillation and the interventions; combined anticoagulation and antiplatelet therapy.

- Ongoing trials were sought in ClinicalTrials.gov, National Institute for Health Research (NIHR) Clinical Research Network Portfolio, Current Controlled Trials (CCT) and the WHO International Clinical Trials Registry Platform (ICTRP).
- Reference lists from identified systematic reviews were checked.
- Citations of relevant studies were examined.
- Further information was sought from clinical experts.

All study types were sought. Searches were not limited by language or date and were carried out during September 2010 by an information specialist.

Search strategies used in the bibliographic databases can be found in *Appendix 2*.

Scoping searches were undertaken to identify completed and ongoing systematic reviews from the following resources: The Cochrane Library [Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, CENTRAL and NHS Economic Evaluation Database (NHS EED)], Aggressive Research Intelligence Facility (ARIF) database of reviews, HTAi portal, MEDLINE (Ovid) 1950 onwards and EMBASE (Ovid) 1980 onwards. The systematic reviews were used to check if there were additional relevant studies.

Study selection

All records identified in the searches were imported into a Reference Manager database (Reference Manager v.11, Thomson ResearchSoft, San Francisco, CA, USA). Duplicate entries were allowed to be removed by the inbuilt feature in Reference Manager and also removed when encountered by reviewers.

Owing to the number of retrieved records and the complexity of the publications, a three-stage process was used to select the studies for review.

Stage 1

The aim was to exclude obviously irrelevant records. The titles of all records were scanned by one reviewer and the record retained if it was about an article/study that met ANY of the following criteria:

- any AF study
- any stroke study
- any study with a group of patients on ACT, APT or both.

Study design or publication type was not an exclusion criterion for this stage.

Stage 2

Based on the title and abstract where available, records were retained if they were about an article/study that adhered to *all* of the following criteria:

- any AF population receiving ACT, APT, or both
- indicated effectiveness data were reported.

Study design or publication type was not an exclusion criterion for this stage.

In the first instance, this stage was undertaken by two reviewers independently; however, it became clear that complexity of the information in the records and particularly absence of detail were leading to far from ideal agreement between the two reviewers (Cohen's kappa coefficient = 0.51). For this reason all records for which discord occurred were screened independently by two further reviewers and any disagreements at this level were resolved by discussion.

All articles progressing through to this stage were obtained in hard copy.

Stage 3

The hard copies were assessed for inclusion in the review against the following criteria. All criteria had to be met to warrant inclusion.

- **Study design** RCTs, non-randomised comparisons, cohort studies, case series or registries, longitudinal studies, systematic reviews and meta-analyses, and conference abstracts published after 2008.
- **Population** Patients with AF, aged ≥18 years. Publications were included, even if a subgroup of patients in the study conformed to this criterion.
- **Intervention** Publications were included only if there was a subgroup of, or complete cohort of, patients on combined ACT and APT. Publications in which the INR of ACT was not specified were also included.
- **Comparator** ACT alone or ACT plus placebo.
- **Outcomes** All-cause mortality and/or at least one vascular event(s) [non-fatal and fatal ischaemic stroke, TIA, systemic embolism (SE)] SE (pulmonary/peripheral arterial embolism), MI, in-stent thrombosis, vascular death, bleeding (major, non-major, minor), reported for both intervention and comparator groups.

If any of the following criteria were met, then the article was excluded:

- **Study design:** All case studies, bridging therapy studies with heparin, rationale or study design papers, ecological studies, case–control studies, cross-sectional studies (surveys), conference abstracts published before 2008, commentaries, and letters or communications were excluded.
- **Population:** Articles that specified a population as having a $CHADS_2$ score of <2 or stroke patients with AF for whom outcomes were retrieved retrospectively, or a population with valve replacement or mechanical heart valves. If $CHADS_2$ scoring or any other stroke risk scoring was not specified, then this was not a reason to exclude an article.

Part-translation of articles not fully published in the English language was obtained to facilitate selection.

The criteria were applied by two reviewers independently and disagreements were resolved by discussion and with the involvement of a third reviewer if required. The reason(s) for the exclusion of articles were recorded.

Where there was more than one unique article from a single study the articles were grouped together for reviewing purposes.

Systematic reviews and meta-analyses that met the inclusion criteria were not reviewed but were utilised to identify further articles. Articles identified in this way were entered in to the Reference Manager database and subjected to the same selection process outlined above.

Data extraction

Data were extracted into a standard form in Microsoft Excel 2007 v.12 (Microsoft Corporation, Redmond, WA, USA) from the main and supporting publications (where relevant) of all included primary studies by one reviewer. A second reviewer checked the accuracy of extracted information. Disagreements were resolved by consensus or by referral to a third reviewer if necessary.

Information regarding study design (including intervention/comparators) and characteristics of study participants was extracted. This included antithrombotic regimens used [anticoagulant ± antiplatelet(s) or placebo], type of ATT used and dose, target INR values used, indication for ATT (e.g. AF ± ACS or stent implantation), study setting (country), study design, sample size, patient inclusion and exclusion criteria, patient characteristics (e.g. age, sex, type and duration of AF, anticoagulant naive or experienced), comparability of patients between different arms (for RCTs and non-randomised trials), primary outcome

measures, secondary outcome measures, length of follow-up, statistical methods used, effect sizes and uncertainty.

Data on the following outcomes were sought from included studies.

Primary outcome measures

Vascular event – stroke (non-fatal and fatal ischaemic), TIA, SE (pulmonary embolism, peripheral arterial embolism), MI, in-stent thrombosis and vascular death (from any of the aforementioned vascular events).

Secondary outcome measures

All-cause mortality and bleeding (major bleeding events, clinically relevant non-major bleeding events, minor bleeding), health-related quality of life, major adverse events (composite of all-cause mortality, non-fatal MI and stroke), revascularisation procedures (e.g. PCI, coronary artery bypass graft surgery, embolectomy) and percentage of time in therapeutic INR range.

Definitions of these outcomes as used in each study were also extracted where reported.

Data for any outcomes other than those listed above were also extracted if it was considered relevant to this report.

Quality assessment

The quality of included studies was assessed by one reviewer. A second reviewer checked the accuracy of extracted information. Disagreements were resolved by consensus or by referral to a third reviewer if necessary.

The methodological quality of RCTs was assessed in terms of the randomisation process, allocation concealment (adequate, unclear, inadequate or not used), degree of blinding, particularly of the outcome assessors, and patient attrition rate, using the Cochrane Collaboration risk of bias assessment tool.[37]

The quality assessment of studies undertaking non-randomised comparisons was undertaken using the Centre for Reviews and Dissemination (CRD)'s checklist for cohort studies.[38] Information on the following was captured: method of outcome measurement, blinding of assessors, whether or not outcome definitions were clearly explained, and which parts of the study were prospective. In addition, the following topic-specific data that were considered relevant to the quality of the studies were assessed: 'Were the indications for use of APT given?' and 'Was it clear whether patients were on APT at the start or commenced such therapy during the observation period?'

Data from randomised studies that were obtained from non-randomised comparisons were classed and treated as non-randomised data. For example, when data from a subset of patients in two or more arms of a RCT were combined to compare with data from another subset of patients obtained from these or other arms of the same study.

From non-randomised comparisons the potential for confounding by indication was ever present; whereby APT was added to ACT, based on clinical judgement of a potential risk of adverse outcomes in some patients if such therapy was not given. Conversely, in those without such perceived risk APT may not have been given. Thus, the patients receiving anticoagulation alone would differ from those receiving the combined therapy, and thus any comparison between the two would be confounded.

Data analysis/synthesis

Outcomes of interest

Selected outcomes of interest were specified in the review protocol, based, in part, on the briefing document produced by the NIHR. These were as shown below.

Primary outcome measures

- Vascular events:
  - non-fatal and fatal ischaemic stroke
  - TIA
  - SE (pulmonary embolism, peripheral arterial embolism)
  - MI
  - in-stent thrombosis
  - vascular death (from any of the above mentioned vascular events).

Secondary outcome measures

- All-cause mortality.
- Bleeding:
  - major bleeding events
  - clinically relevant non-major bleeding events
  - minor bleeding.
- Health-related quality of life.
- Major adverse events.
- Revascularisation procedures.
- Percentage of time within therapeutic INR range (where available).

Although definitions of these outcomes could have been described rigidly for this review (such as using the definitions of the International Society on Thrombosis and Haemostasis[39]) it was decided to retain and record the definitions used in the original papers and to group data accordingly. Setting aside issues around non-reporting or poor reporting of definitions, for most outcomes this was fairly straightforward. However, there were instances for which judgement was required. For example, for the outcome of SE a few studies referred to TE and it was assumed from the definitions of outcomes provided by the studies that TE referred to arterial TE, not venous TE, and thus data from these studies were grouped with SE from similar studies.

For the outcomes of interest, data were not available for all.

Handling data and presentation of results

Owing to the paucity of evidence from randomised studies, data from non-randomised and/or observational designs were also included in this review. Evidence from different study designs was not combined.

The comparison of interest was between combined anticoagulation and APT and ACT alone.

For dichotomous outcomes, data from randomised studies are presented as proportions, percentages and relative risks (RRs) [± 95% confidence interval (CI)] for comparisons. RRs and 95% CIs were calculated using Review Manager (RevMan v.5.1: The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Dichotomous data from non-randomised comparisons are not presented as RRs, given the potential for confounding by indication within such studies. If continuous outcome data had been encountered, they would be represented as differences in means or means.

Where available, data were presented for the longest follow-up available in each study. Data for follow-up assessments less than this are also presented, where appropriate. In many cases only mean/median follow-up durations were reported by studies.

Studies were considered to directly compare anticoagulation plus APT with ACT alone if the anticoagulant was the same in both arms, and there were no other treatment-related differences between arms.

Different anticoagulation therapies were considered separately. Different APTs were also considered separately. As ACT can be a fixed or adjusted dose it was decided a priori on clinical advice to report these regimes separately. A priori it was decided that only the following groups could be considered as classes of intervention. VKAs were considered as a class of intervention and, thus, reported together and where possible pooling of data across the class was considered if there was sufficient methodological and clinical homogeneity between studies. Oral direct thrombin inhibitors (ODTIs) were also considered as a class of intervention. None of the APTs was considered as a class.

Although planned, pooling of results was not attempted for the assessment of effectiveness of individual technologies because of the substantial clinical and methodological heterogeneity between studies and the confounding by indication inherent in the observational studies.

Assessment of publication bias

The number of relevant studies for a given comparison was too small to allow formal assessment of publication bias.

Ongoing studies

A number of ongoing studies were identified in the searches. They were not included in the systematic review, but discussed in *Chapter 4* (see *Strengths and limitations*, *Ongoing studies*) to aid updating and extension of this review.

Sensitivity and subgroup analysis

Although the number of subgroups and/or sensitivity analyses might have been possible in this report, none was undertaken owing to lack of data.

Changes to protocol

The protocol specified that, where possible, the relevant target INR for the combined ACT-plus-APT treatment arm should be 2.0–3.0 as recommended by ESC guidelines.[2] However, it was felt that this criterion might be too restrictive or the range not reported. Therefore, this criterion was relaxed to allow inclusion of studies with either a different target range or an unspecified target INR range.

It was intended and specified in the protocol that an individual participant data (IPD) meta-analysis would be performed to specifically address the effect of APT added to ACT compared with ACT alone on (1) time to first vascular event; (2) time to first major haemorrhage or clinically relevant bleed; (3) death; and (4) time within therapeutic INR range. Predefined subgroup analyses were to be developed to possibly include the following: (1) stent type (bare metal vs drug eluting); (2) warfarin-naive subjects compared with warfarin-experienced subjects; (3) short- and long-term outcomes; (4) patients with diabetes mellitus; and (5) a $CHADS_2$ score of ≥ 2 and < 2. Data were to be requested either in electronic or paper from triallists and subjected to consistency checks.

However, there was a paucity of evidence from the included studies for many of these analyses, and where some data were available it was clear that the methodological heterogeneity between studies, and the clinical heterogeneity within and between studies, was against such analyses. It was therefore agreed with the NIHR not to perform the IPD analysis (for further explanation, see *Chapter 4*, *Strengths and limitations*).

An additional stage of study selection was added (Stage 2 is described above – see *Study Selection*) because of the high yield of relevant studies from the preceding stages. In this new stage, selection criteria

were based on those determined a priori for the whole review and thus unbiased. This new selection stage came before obtaining full copies of articles and the application of all of the inclusion/exclusion criteria for the review.

Reporting findings

In the following sections based on clinical input, the findings of the review are structured by outcome (and subcategories of outcome where relevant) and then for each outcome by intervention–comparison (including division by whether ACT was by adjusted or fixed dosing), with further subdivision by risk attributed to the populations where relevant. Data from randomised comparisons are the primary evidence presented with supplementary information given from pooled analyses and/or non-randomised comparisons where this information adds to that from the randomised comparisons (i.e. longer follow-up). However, caution is applied with the use of non-randomised data given that the findings are highly likely to be confounded by indication. A summary section is provided where the findings are presented by intervention and comparator, and then for each of these the data for the review outcomes are presented. Presenting the data in both ways allows access to information depending on whether the perspective required is that of the outcomes or the comparisons.

Chapter 3 Results

Quantity and quality of research available

Figure 2 illustrates the study selection stages. The combined bibliographic database search yielded 13,519 citations. After the removal of records for non-relevant articles and duplicate entries, full texts of 633 potentially relevant articles were sought. The authors of 12 studies were contacted, as copies of the study reports were difficult to obtain. Seven of these were still unobtainable after this procedure. Details of these studies are presented in *Appendix 3*. The 626 full articles were assessed against the criteria for inclusion in the review by two reviewers independently. A total of 53 publications met the criteria (see *Figure 2*). A list of excluded publications along with reason(s) for their exclusion can be found in *Appendix 4*.

No ongoing studies comparing combined ACT plus APT with ACT alone were identified in the searches. In the discussion chapter (see *Chapter 4*), there is a section on the pre-defined subgroup analysis of the ongoing or recently completed Phase III clinical trials identified by the steering committee.

Characteristics of included studies

Of the 53 included publications (*Figure 3*),[20,39–90] 18 were reports of systematic reviews or meta-analyses[20,74–90] which added no further data to the remaining 35 articles (see *Figure 2* and *Appendix 5*).[39–73] Of the latter, five articles[39–43] each reported randomised controlled studies between ACT plus APT and ACT alone. Three of these RCTs were supported by post hoc, subgroup or pooled analyses reported in a further six articles.[44–49] The characteristics of these studies and their quality assessment are reported in *Tables 4* and *5*, respectively, and in *Appendix 6*.

The remaining 24 articles[50–73] consisted of 18 primary studies reporting non-randomised comparisons for the therapies of interest. Of these, 14 studies[50–63] (in 14 articles) reported data from observational designs, both prospective[50–55] and retrospective[56–63] in nature. The remaining four studies in 10 articles[64–73] were originally designed to assess the effectiveness of an anticoagulant without additional APT. However, these were included because they reported data on a subgroup of patients treated with combined anticoagulant plus APT. The characteristics of these studies and their quality assessment are reported in *Tables 6* and *7*, respectively.

Of the included studies, three RCTs[40,42,43] and 14 other studies reporting non-randomised comparisons summarised data for warfarin therapy in different regimes plus an APT compared with warfarin.[50–53,55–57,59–65] One RCT[39] and one non-randomised study[54] reported data on acenocoumarol (Sinthrome®, Alliance) plus an APT compared with acenocoumarol alone. The remaining one RCT[41] reported data on fluindione plus aspirin compared with fluindione plus placebo.[41] One study[72] reporting non-randomised comparisons used idraparinux, and one used dabigatran (Pradaxa®, Boehringer Ingelheim) as anticoagulant agent,[73] whereas two studies[64,65] reported data on ximelagatran plus warfarin compared with ximelagatran alone. Doses of APT varied between studies.

Of the included RCTs, three[39,42,43] used therapies in an open-label fashion, whereas this information was not clear in one.[40] Assessors were blinded in three[39,41,42] out of five RCTs,[39–43] and intention-to-treat (ITT) analysis was undertaken in three studies.[40,42,43] However, two of these studies were terminated prematurely.[41,42] The sample size varied from 43 to 1209 participants in the RCTs,[39,40] with variable periods of follow-up (22 days[40] to 42 months[42]).

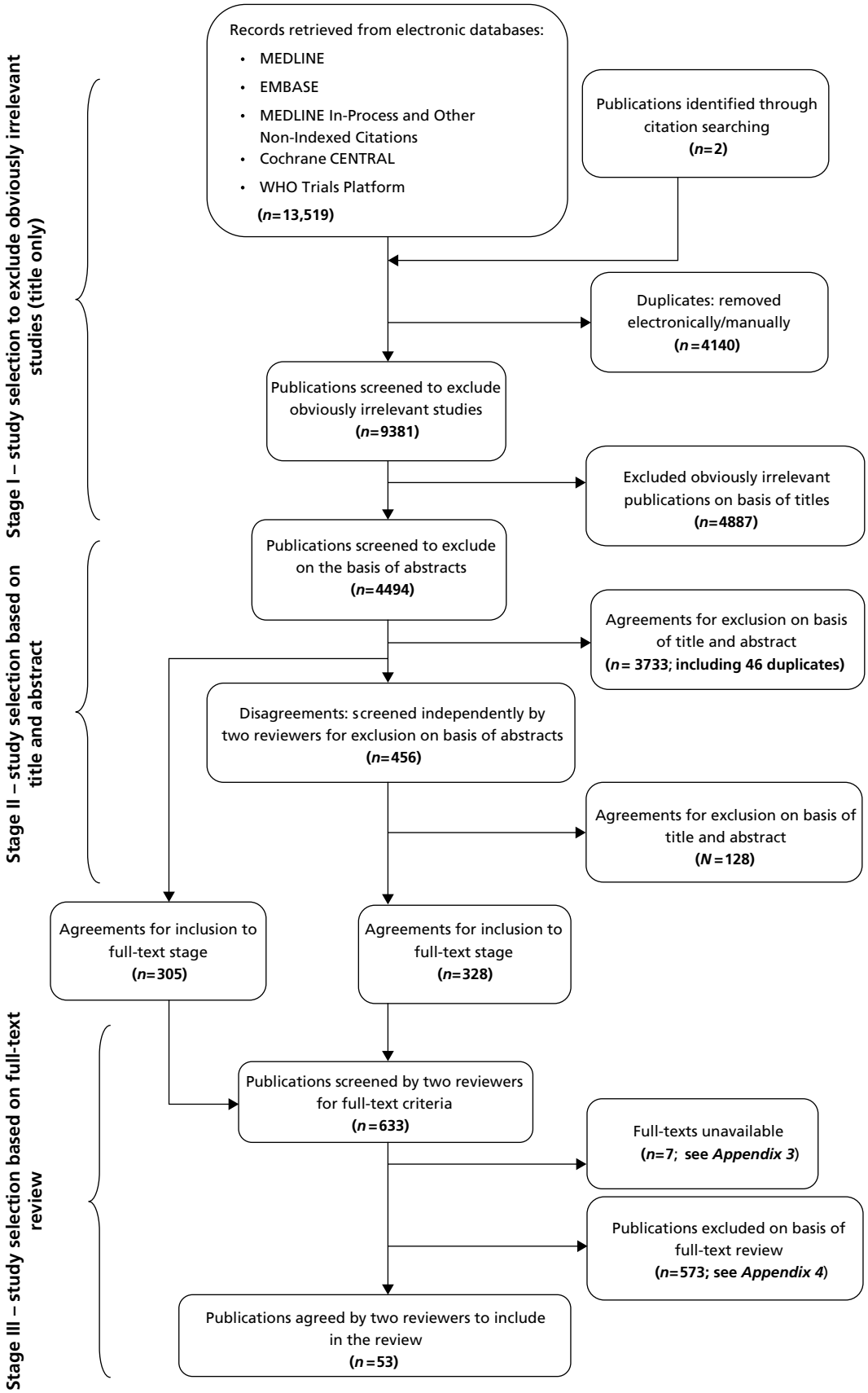

FIGURE 2 Study selection.

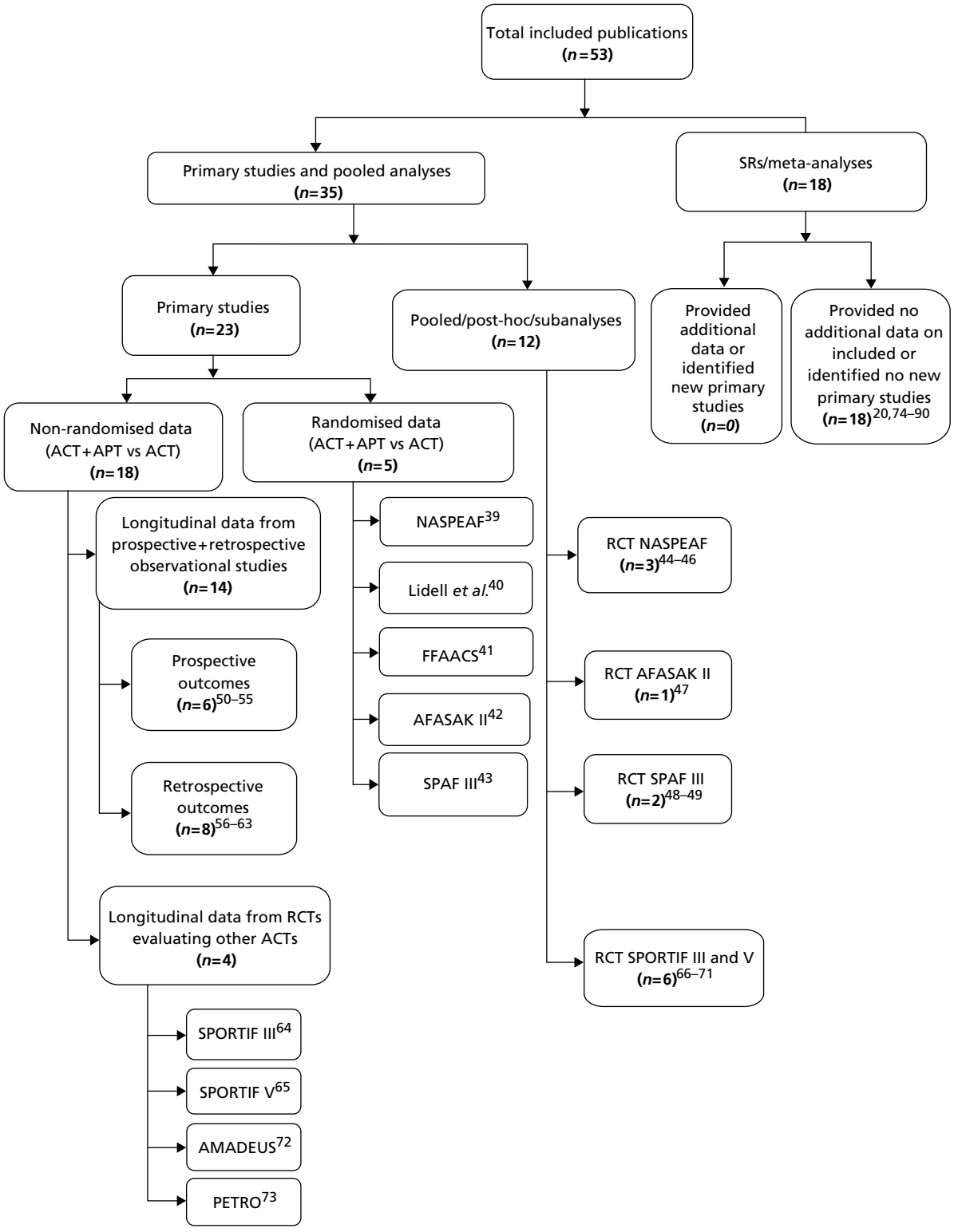

FIGURE 3 Included studies. AFASAK II, Second Copenhagen Atrial Fibrillation, ASpirin and Anticoagulation Study; AMADEUS, Comparison of fixed-dose idraparinux with conventional anticoagulation by dose-adjusted oral vitamin K antagonist therapy for prevention of thromboembolism in patients with atrial fibrillation; FFAACS, Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontané study; NASPEAF, NAtional Study for Prevention of Embolism in Atrial Fibrillation; PETRO, dabigatran with or without concomitant aspirin compared with warfarin alone in patients with non-valvular atrial fibrillation study; SPAF III, Stroke Prevention in Atrial Fibrillation III study; SPORTIF, Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation.

Of the studies reporting non-randomised comparisons, six were retrospective,[56–58,60–63] and the time of APT use varied between the studies. The majority of these studies consisted of a retrospective review of medical records where prior knowledge of allocation of therapy was not possible.[50–53,56–61,63] However, all but five studies[50,55,59,62,73] clearly reported the criteria by which APT was used in the study. Of note is the study by Ezekowitz *et al*.[73] [PETRO (Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with non-valvular atrial fibrillation)], in which it was difficult to identify if APT was used at random or indicated in a subgroup. For this reason, the study is classified as a non-randomised comparison of ACT plus APT and ACT only.

Between-study differences

The subsequent sections will report the event rates for each outcome. Methodological heterogeneity exists between the included studies that may explain any differences in the event rates reported. Rather than repeat these methodological differences for each and every outcome of interest, the reader will be referred to the following discussion of these differences. Where specific differences in the methodology between the included studies are apparent, which are important to highlight and/or only pertinent to that particular outcome, these differences will be specified under that outcome.

The differences in the event rates reported by the included studies may reflect differences in the population risk profile, with some studies including high-risk AF populations (three RCTS[39,41,43] and seven non-randomised comparisons[50,55,58,64,65,72,73]) and/or intermediate-risk patients with AF (one RCT[39]), whereas other studies did not report the risk profile of included patients (two RCTs[40,42]) and 11 other non-randomised comparisons.[51–54,56,57,59–63]

The sample size also varied considerably between included studies, from 43 participants in one RCT[40] to 118,606 in a large non-randomised comparison.[63] As a result of the overall sample size, the number of patients receiving combined ACT and APT and the comparator also varied considerably, with only 34 patients receiving the combination therapy in Bover *et al*.,[54] between 21 and 36 patients receiving the various permutations of ACT plus APT in the PETRO study,[73] and 76 patients receiving combination therapy and 81 receiving ACT alone in the FFAACS (Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontané) trial,[41] which will have influenced the reported event rates for each outcome.

Further, the included studies comprise both randomised and non-randomised data. Among non-randomised comparisons there is the potential for confounding by indication with the use of APT, as this was often given at the discretion of the treating physician, with patients at high risk of a vascular event and/or those less likely to bleed receiving combination therapy. Indeed, Bover *et al*.[54] reported that the patients receiving combined therapy were at a higher risk of stroke than those who were administered adjusted-dose acenocoumarol (INR 2.0–3.0) alone. Moreover, the number of patients with previous experience of an anticoagulant agent or APT in each study may also affect the event rate, for example patients who can tolerate either ACT or APT will continue on such therapy and therefore may be less likely to bleed on treatment than those who experience a bleed and therefore discontinue such therapy – 'ATT survivor'.

The included studies also compared different types of anticoagulant and APT in various permutations, which makes comparison of event rates across studies using different interventions and comparators difficult. Studies compared a VKA, either warfarin,[40,42,43,50–53,55–57,63–65,72] acenocoumarol,[39,54] or fluindione[41] in combination with either aspirin[41–43,50,51,53–58,60–65,72,73] or other antiplatelet agents, such as triflusal,[39,54] clopidogrel,[40,63] or dual APT of aspirin plus clopidogrel.[63] Furthermore, two other studies compared an ODTI (anticoagulant) – either ximelagatran[64,65] or dabigatran[73] – in combination with aspirin (in different doses) or alone.

Among those studies comparing VKAs plus aspirin to a VKA alone,[39–43,50–54,54–57,59–65,67,69,72] different VKA regimes were used in the combination therapy arm, either fixed dose (1.25 mg[42]) or adjusted dose to maintain a target INR range [e.g. INR 1.2–1.5,[43] INR 2.0–3.0,[40,64,65] INR 1.9–2.5,[54] INR 2.0–2.6,[41] INR 1.4–2.4 (high risk) and INR 1.25–2.0 (intermediate risk)[39]]. Of the included RCTs, therapies were administered

in either an open-label[42,43] or in a double-blind fashion.[41] In addition, the APT also varied (aspirin, triflusal, clopidogrel, and aspirin plus clopidogrel). In the studies reporting randomised comparisons, aspirin was utilised in different doses (300 mg,[42] 325 mg[43] and 100 mg[41]), and also in non-randomised comparisons (≤ 100 mg,[64,65,72] 100 mg,[61] 81 or 325 mg[73] and dose not specified in others[51,53,56–58,62]). Similarly, other antiplatelets were used in different doses such as triflusal (600 mg,[39] 600 mg and 300 mg[54]), clopidogrel (75 mg:[40] dose not specified[63]) and dual APT of aspirin plus clopidogrel (dose not specified[50,63]), which makes direct comparison between studies difficult.

In addition, some randomised studies used the same target INR range in both the intervention and comparator arm (RCTs[40,41] besides non-randomised comparisons[54,51,53, 56,57,59,61,62,64,65,72]), whereas others did not (RCTs[39,42,43] and non-randomised comparisons[54,55]), again making difficult the direct comparison between the intervention and comparator arms within the studies. However, the majority of studies did use the standard therapeutic INR target of 2.0–3.0 in the comparator arm[40,41,51,53–55,57,59,61,62,64,65,72] whereas others did not, although only four studies[39,40,43,54] reported time in therapeutic range (TTR).

There were also differences across studies in the definitions of the outcomes of interest used and these differences are discussed, where relevant, under each outcome.

Furthermore, the considerable variation in the length of follow-up (e.g. 22 days[40] to 4.92 years[54]) in each of the included studies may have influenced event rates. The combination of a short duration of follow-up for outcomes that are not particularly common together with a small sample size may have resulted in studies being underpowered. Of note the AFASAK II study (Second Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation Study)[42] was prematurely terminated when results of the SAAF III (Stroke Prevention in Atrial Fibrillation) trial,[43] demonstrating the superiority of adjusted-dose warfarin (INR 2.0–3.0) alone, over combination of adjusted-dose warfarin (INR 1.2–2.5) and aspirin 325 mg in preventing stroke or SE, were published. Further, the FFAACS study[41] was also terminated early due to poor recruitment. It should also be noted, that Bover *et al*.[54] was a non-randomised comparison that followed up of a proportion of the patients enrolled in the NASPEAF (National Study for Prevention of Embolism in Atrial Fibrillation) study[39] (although it is not clear how many patients from NASPEAF were included in Bover *et al*., within each arm of the latter study), with addition of newly recruited participants, over a longer period of time.

Moreover, the temporal changes in the management of AF over the last 20 years may have influenced the event rate reported in studies enrolling patients in the early 1990s (AFASAK II[42] and SPAF III[43]) compared with those from 2000 onwards.[39,40,41,54,63,64,65,73]

TABLE 4 Characteristics of studies reporting randomised comparisons

Author, date (name of trial), location, no. of centres	Study duration (mean), randomisation design, no. of patients randomised	Intervention (ACT + APT), no. of patients	Comparator (ACT only or ACT + placebo), no. of patients	Inclusion criteria; stroke risk	Age (years): mean (SD, range), % male
[a]Pérez-Gómez *et al.*, 2004 (RCT – NASPEAF), multicentre[39]	33 months, parallel, open label, $n = 1209$	Adjusted-dose acenocoumarol (INR 1.25–2.0) + triflusal (600 mg), $n = 222$ (intermediate risk) Adjusted-dose acenocoumarol (INR 1.4–2.4) + triflusal (600 mg), $n = 223$ (high risk)	Adjusted-dose acenocoumarol (INR 2.0–3.0), $n = 237$	Age ≥ 18 years; high risk of stroke[b] or intermediate risk of stroke[c]	68.6;[d] 45.6
Lidell *et al.*, 2003, Sweden, four centres[40]	22 days, parallel, double blind, placebo controlled, $n = 43$	Adjusted-dose warfarin (INR 2.0–3.0) + clopidogrel (75 mg); $n = 20$	Adjusted-dose warfarin (INR 2.0–3.0) + placebo, $n = 23$	Age 35–75 years, NVAF, receiving warfarin for ≥ 2 months; no stroke risk factors reported	66.6;[d] 81.4
Lechat *et al.*, 2001, (RCT – FFAACS), France, multicentre[41]	0.84 years, parallel, double blind, placebo controlled, $n = 157$	Fluindione (INR 2.0–2.6) + aspirin (100 mg), $n = 76$	Fluindione (INR 2.0–2.6) + placebo, $n = 81$	NVAF; high risk of stroke[e]	73.7;[d] 50
[f]Gullov *et al.*, 1998, (RCT – AFASAK II), Denmark, single centre[42]	42 months, parallel, open label, $n = 677$	Fixed-dose warfarin (1.25 mg) + aspirin (300 mg); $n = 171$	Fixed-dose warfarin (1.25 mg/day), $n = 167$ Adjusted-dose warfarin (INR 2.0–3.0), $n = 170$	Age ≥ 18 years with chronic NVAF; no stroke risk factors reported	76.5 (6.9, 44–89), 60
[g]Stroke Prevention in Atrial Fibrillation Investigators, 1996 (RCT – SPAF III), USA and Canada, 20 sites[43]	1.1 years, parallel, open label, $n = 1044$	Fixed-dose warfarin (INR 1.2–1.5) + aspirin (325 mg), $n = 521$	Adjusted-dose warfarin (INR 2.0–3.0), $n = 523$	Age ≥ 18 years with NVAF, eligible 30 days from occurrence of stroke/TIA; high risk of stroke[h]	72 (9); 61

NVAF, non-valvular atrial fibrillation.

a Supported by three subgroup analyses[44–46] of the same population (on same intervention and comparators).

b Either NVAF with prior embolism or those with mitral stenosis with and without prior embolism.

c NVAF with no embolism at baseline.

d Standard deviation and range for age not reported.

e Presence of at least one of the following: history of TE (TIA, non-disabling ischaemic stroke or peripheral embolism) or aged >65 years and at least one of history of hypertension [systolic arterial pressure > 160 mmHg or diastolic arterial pressure > 90 mmHg); recent episode (<3 months previously) of congestive HF or alteration in left ventricular function (echocardiographic left ventricular shortening fraction <25% or LVEF <40% within 3 months before study inclusion).

f Supported by one analysis[47] of the same population (on same intervention and comparators).

g Supported by two analyses[48,49] of the same population (on same intervention and comparators).

h Presence of at least one of the following: impaired LV function manifested by: recent (≤ 100 days) congestive heart disease or fractional shortening of ≤25% by M-mode echocardiography; systolic blood pressure of >160 mmHg at study entry: prior ischaemic stroke, TIA or SE (i.e. prior TE), female and age >75 years.

TABLE 5 Quality assessment of studies reporting randomised comparisons

Author, date (name of the trial) duration (mean)	Truly random allocation and sequence generation, method	Adequate allocation concealment	Blinding	Use of ITT	Dropouts and withdrawals, *n* (%)	Percentage on ACT before study	Comments
[a]Pérez-Gómez *et al.*, 2004 (RCT – NASPEAF), 33 months[39]	Yes, computer generated, centrally administered	No[b]	Yes[c]	No	Withdrawals, 18.3%; lost to follow-up, 50 (4.14)	NR	Withdrawals resulted in switch over from combined treatment to ACT in 56 patients
Lidell *et al.*, 2003, 22 days[40]	Not clear, NR	Unclear	Unclear	Yes	Withdrawals and lost to follow-up, 0	NR	Arbitrary sample size used
Lechat *et al.*, 2001 (RCT – FAACS), 0.84 years[41]	Yes, centrally performed randomisation through fax transmission of the inclusion form	Yes	Yes[c]	No	Withdrawals,30; deaths, 6; lost to follow-up, 0	85	Small sample size; premature termination of trial due to low event rate and recruitment rate
[d]Gullov *et al.*, 1998, (RCT – AFASAK II), 42 months[42]	Yes, computerised randomisation	No[b]	Yes[c]	Yes	Withdrawals, 112 (16.5%); dropout, 58 (8.6)	0	Premature termination after publication of SPAF III[43] results
[e]Stroke Prevention in Atrial Fibrillation Investigators, 1996 (RCT – SPAF III), 1.1 years[43]	Yes, stratified by study centre and sequence could not be previewed	No[b]	Not clear[f]	Yes	Withdrawals, 72 (6.9%); lost to follow-up: 0	56	Multiple laboratories with reagents of varying sensitivities used for INR measurements; trial terminated in interim analysis (after mean follow-up of 1.1 years) as adjusted-dose warfarin was found superior to combined therapy; diabetes mellitus not considered as one of the stroke risk factors

NR, not reported.

a Supported by two subgroup analyses[44–46] of the same population (on same intervention and comparators).

d Supported by one analysis[47] of the same population (on same intervention and comparators).

e Supported by two analyses[48,49] of the same population (on same intervention and comparators).

b Open-label administration of therapies.

c Assessors blinded.

f Patients with events were evaluated by neurologists affiliated to study but not engaged in follow-up and unaware of assigned therapy, but found out drug regimen in 27% of primary events diagnosed (ineffective blinding of assessors).

TABLE 6 Characteristics of studies reporting non-randomised comparisons

Author, date; study source; location; no. of centres	Study duration mean (SD, range); prospective/ retrospective; no. of patients	ACT (INR or dose) + APT (dose), no. of patients	ACT only (INR or dose), no. of patients	Inclusion criteria; stroke risk	Age (years): mean (SD, range), percentage males
Hansen *et al.*, 2010; registry; Denmark; nationwide registries[63]	3.3 (2.6) years; retrospective; $n = 118,606$	Warfarin[a] + aspirin,[a] 18,345 Warfarin[a] + clopidogrel,[a] 1430 Warfarin[a] + aspirin[a] + clopidogrel,[a] $n = 1261$	Warfarin,[a] $n = 50,919$	Age ≥ 30 years, surviving first-time hospitalisation for primary or secondary diagnosis of AF, discharge prescription of warfarin, aspirin, clopidogrel Stroke risk NR	73.7 (12.3); 52.4
[b]Bover *et al.* 2009 to $n = 574$; 4.2 years[54]	4.92 years; prospective; $n = 574$	Acenocoumarol (INR 1.9–2.5) + triflusal (600 mg), $n = 155$ Acenocoumarol (INR 1.9–2.5) + triflusal (300 mg), $n = 120$ Acenocoumarol (INR 1.9–2.5) + aspirin (100 mg), $n = 34$	Acenocoumarol (INR 2.0–3.0), $n = 265$	Patients who had undergone at least 12 months of follow-up	68.6; 45.6
Lopes *et al.*, 2009; cohort of RCT – APEX AMI; USA, Europe, Australia, NZ and Canada; 296 sites[50]	90 days; prospective; $n = 276$	Warfarin[a] + aspirin[a] + clopidogrel,[a] $n = 37$	Warfarin,[a] $n = 59$	Age ≥ 18 years Stroke risk high[c]	52–81
Abdelhafiz and Wheeldon, 2008; anticoagulation clinic referrals; UK; one hospital[51]	19 (8.1, 1–31) months; prospective; $n = 402$	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin,[a] $n = 8$	Adjusted-dose warfarin (INR 2.0–3.0), $n = 394$	New NVAF patients referred by GP Stroke risks NR	72.3; 55.72
Amadeus Investigators, 2008, cohort of RCT – AMADEUS; Australia, Canada, Denmark France, Italy, New Zealand, Poland, Netherlands, UK and the USA; 165 centres[72]	311 days; prospective; $n = 4576$	Idraparinux or adjusted-dose VKA[d] (INR 2.0–3.0) + aspirin (≤ 100 mg), $n = 971$	Idraparinux (2.5 mg), $n = 2283$; adjusted-dose VKA[d] (INR 2.0–3.0), $n = 2293$	NVAF and indication for long-term anticoagulation ≥ 1 stroke risk factor[e]	70.1 (9.1); 66.5

Author, date; study source; location; no. of centres	Study duration mean (SD, range); prospective/ retrospective; no. of patients	ACT (INR or dose) + APT (dose), no. of patients	ACT only (INR or dose), no. of patients	Inclusion criteria; stroke risk	Age (years): mean (SD, range), percentage males
Ezekowitz *et al.*, 2007; cohort of RCT – PETRO; Denmark, the Netherlands, Sweden, and the USA; 53 centres[73]	12 weeks, prospective; $n = 502$	Dabigatran (50 mg b.i.d.) + aspirin (81 mg), $n = 21$ Dabigatran (50 mg b.i.d.) + aspirin (325 mg), $n = 27$ Dabigatran (150 mg b.i.d.) + aspirin (81 mg), $n = 36$ Dabigatran (150 mg b.i.d.) + aspirin (325 mg), $n = 33$ Dabigatran (300 mg b.i.d.) + aspirin (81 mg), $n = 34$ Dabigatran (300 mg b.i.d.) + aspirin (325 mg), $n = 30$	Dabigatran (50 mg), $n = 105$ Dabigatran (150 mg), $n = 166$ Dabigatran (300 mg), $n = 161$	Documented AF + CAD ≥1 stroke risk criteria[f]	70 (8.3); 81.9
Suzuki *et al.*, 2007; database of cardiovascular clinic; Japan; one centre[56]	1 year, retrospective; $n = 667$	Adjusted-dose warfarin (INR 1.6–2.6) + aspirin,[a] $n = 210$	Adjusted-dose warfarin (INR 1.6–2.6), $n = 457$	NVAF patients on warfarin Stroke risks NR	68.4 (10.6); 66.6
Burton *et al.*, 2006; patient records from GPs; Scotland; 27 practices[57]	42 months; retrospective; $n = 601$	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin,[a] $n = 18$	Adjusted-dose warfarin (INR 2.0–3.0), $n = 309$	Patients with persistent AF Stroke risks NR	77; 51.1
Stenestrand *et al.*, 2005; registry; Sweden; 72 hospitals[58]	1–8 years; retrospective; $n = 5616$	OAC[a,g] + aspirin,[a] $n = 479$	OAC,[a,g] $n = 1369$	AF on the discharge ECG and AMI as final diagnosis; stroke risk high[h]	77.7; 62.43
SPORTIF V investigators, 2005; cohort of RCT – SPORTIF V; USA, Canada; 409 sites[65]	20 months (5.1, 0–31); prospective; $n = 3992$	Ximelagatran (36 mg b.i.d.) + aspirin (<100 mg), unclear Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (≤100 mg), unclear	Ximelagatran (36 mg b.i.d.), $n = 1960$ Adjusted-dose warfarin (INR 2.0–3.0), $n = 1962$	Persistent or paroxysmal NVAF patients; high risk[e]	72 (9.1); 69
SPORTIF III Investigators, 2003; cohort of RCT – SPORTIF III cohort; Europe, Asia, Australasia; 259 hospitals[64]	17.4 (4.1) months; prospective; $n = 3407$	Ximelagatran (36 mg b.i.d.) + aspirin (<100 mg), unclear Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (≤100 mg), unclear	Ximelagatran (36 mg b.i.d.), $n = 1704$ Adjusted-dose warfarin (INR 2.0–3.0), $n = 1703$	Persistent or paroxysmal NVAF; high risk[e]	70 (9); 69.1

continued

TABLE 6 Characteristics of studies reporting non-randomised comparisons (*continued*)

Author, date; study source; location; no. of centres	Study duration mean (SD, range); prospective/ retrospective; no. of patients	ACT (INR or dose) + APT (dose), no. of patients	ACT only (INR or dose), no. of patients	Inclusion criteria; stroke risk	Age (years): mean (SD, range), percentage males
Teitelbaum *et al.*, 2008; pooled SPORTIF III and V cohort on warfarin; Asia, EU, Australasia, Canada and the USA; 409 sites and 259 hospitals[66]	16.6 (6.3) months; prospective; *n* = 7329	Ximelagatran (36 mg b.i.d.) + aspirin (<100 mg), unclear Warfarin (INR 2.0–3.0) + aspirin (≤100 mg), unclear	Ximelagatran (36 mg b.i.d.), 3664 Warfarin (INR 2.0–3.0), 3665	Persistent or paroxysmal NVAF; high risk[e]	
Akins *et al.*, 2007; pooled data RCTs – SPORTIF III and V; Asia, EU, Australasia, Canada and the USA; 409 sites and 259 hospitals[67]	16.6 (6.3) months; prospective; *n* = 1539	Ximelagatran (36 mg b.i.d.) + aspirin (≤100 mg), *n* = 157 Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (≤100 mg), *n* = 186	Ximelagatran (36 mg b.i.d.), *n* = 629 Adjusted-dose warfarin (INR 2.0–3.0), *n* = 567	Persistent or paroxysmal NVAF Patients with prior stroke	NR
White *et al.*, 2007; pooled SPORTIF III and V of cohort on Warfarin, Asia, EU, Australasia, Canada and the USA; 409 sites and 259 hospitals[68]	16.6 (6.3) months; prospective; *n* = 3587	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (≤100 mg), *n* = 475	Adjusted-dose warfarin (2.0–3.0), *n* = 3112	Persistent or paroxysmal NVAF high risk[e]	NR
Halperin, 2005; post hoc analysis RCT – SPORTIF III; Europe, Asia and Australasia; 259 hospitals[71]	17.4 (4.1) months; prospective; *n* = 3407	Ximelagatran (36 mg b.i.d.) + aspirin (<100 mg), *n* = 337 Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (≤100 mg), *n* = 290	Ximelagatran (36 mg b.i.d.), *n* = 1367 Adjusted-dose warfarin (INR 2.0–3.0), *n* = 1413	Persistent or paroxysmal NVAF high risk[e]	70 (9); 69.1
Flaker *et al.*, 2006; pooled data RCT – SPORTIF III and V; Asia, EU, Australasia, Canada and the USA; 409 sites and 259 hospitals[69]	16.6 (6.3) months; prospective; *n* = 7304[f]	Ximelagatran (36 mg b.i.d.) + aspirin(≤100 mg), *n* = 531 Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (≤100 mg), *n* = 481	Ximelagatran (36 mg b.i.d.), *n* = 3120 Adjusted-dose warfarin (INR 2.0–3.0), *n* = 3172	Persistent or paroxysmal NVAF high risk[e]	NR
Douketis *et al.*, 2006; pooled data RCT-SPORTIF III and V; Asia, EU, Australasia, Canada and the USA; 409 sites and 259 hospitals[70]	16.6 (6.3) months; prospective; *n* = 7329	Ximelagatran (36 mg b.i.d.) + aspirin (<100 mg), unclear Warfarin (INR 2.0–3.0) + aspirin (≤100 mg), unclear	Ximelagatran (36 mg b.i.d.), *n* = 3664 Adjusted-dose warfarin (INR 2.0–3.0), *n* = 3665	Persistent or paroxysmal NVAF high risk[e]	NR

Author, date; study source; location; no. of centres	Study duration mean (SD, range); prospective/ retrospective; no. of patients	ACT (INR or dose) + APT (dose), no. of patients	ACT only (INR or dose), no. of patients	Inclusion criteria; stroke risk	Age (years): mean (SD, range), percentage males
Johnson *et al.*, 2005; hospital records; Australia; four hospitals[59]	28 months; retrospective; $n = 228$	Adjusted-dose warfarin (INR 2.0–3.0) + APT,[a,g] NR	Adjusted-dose warfarin (INR 2.0–3.0), $n = 228$	Age ≥ 76 years, warfarin at admission and discharge diagnosis of AF Stroke risk NR	81.1 (76–94); 41.7
Blich *et al.*, 2004; primary physician clinics; Israel; 23 clinics[61]	7.2 (5.2, 2–40) years; retrospective; $n = 506$	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (100 mg), NR	Adjusted-dose warfarin (INR 2.0–3.0), NR	Chronic or recurrent paroxysmal NVAF (> 48 hour duration) diagnosed ≥ 2 years Stroke risk NR	75.7 (8.08, 35–100); 55.7
Shireman *et al.*, 2004, database of inpatients discharged from acute-care hospitals; USA; countrywide[60]	90 days or 180 days; retrospective; $n = 10,093$	Warfarin[a] + aspirin/clopidogrel/ ticlopidine/dual APT,[a] $n = 1962$	Warfarin,[a] $n = 8131$	Age ≥ 65 years Warfarin on discharge; AF diagnosis on discharge Stroke risk NR	77.2; 49.6
Klein *et al.*, 2003; cohort of RCT – ACUTE; international sites; 70[62]	8 weeks; prospective; $n = 1222$	Warfarin/heparin (INR 2.0–3.0) + aspirin,[a] $n = 560$	Warfarin (INR 2.0–3.0), $n = 444$ Heparin (INR 2.0–3.0), $n = 524$ Warfarin + heparin adjusted dose (INR 2.0–3.0), $n = 249$	Age > 18 years, AF of > 2 days' duration, candidates for cardioversion, patients with atrial flutter who have a history of AF Stroke risk NR	65.1; 66.67
Hart *et al.*, 2000; cohort of SPAF III; USA and Canada; 20 sites[55]	2 years; prospective; $n = 2012$	Adjusted-dose warfarin (INR 1.2–1.5) + aspirin (325 mg/day), $n = 81$	Adjusted-dose warfarin (INR 2.0–3.0), $n = 91$	High risk of stroke[i]	69 (10); 72
Toda *et al.*,1998; hospitalised patients; Japan; one hospital[52]	7.2 (5.1, 1–23) years; retrospective; $n = 288$	Warfarin[a] + APT,[a,g] $n = 30$	Warfarin alone,[a] $n = 10$	Chronic or paroxysmal NVAF; stroke risk NR	54.6 (13.3, 8–82); 59.0

continued

TABLE 6 Characteristics of studies reporting non-randomised comparisons (*continued*)

Author, date; study source; location; no. of centres	Study duration mean (SD, range); prospective/ retrospective; no. of patients	ACT (INR or dose) + APT (dose), no. of patients	ACT only (INR or dose), no. of patients	Inclusion criteria; stroke risk	Age (years): mean (SD, range), percentage males
Albers *et al.*,1996; hospitalised patient records; USA; six hospitals[53]	NR; retrospective, $n = 309$	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin[a] at admission, $n = 9$ Adjusted-dose warfarin (INR 2.0–3.0) + aspirin[a] at discharge, $n = 22$	Adjusted-dose warfarin (INR 2.0–3.0) on admission, $n = 62$ Warfarin (INR 2.0–3.0) at discharge, $n = 83$	AF documented on admission or during hospitalisation Stroke risk NR	71.6 (12.7); 51

ACUTE, Assessment of Cardioversion Uising Transesophageal Echocardiography; AMADEUS, Comparison of fixed-dose idraparinux with conventional anticoagulation by dose-adjusted oral vitamin K antagonist therapy for prevention of thromboembolism in patients with atrial fibrillation; AMI, acute myocardial infarction; APEX, AMI Assessment of PEXelizumab in Acute Myocardial Infarction; b.i.d., dose administered twice daily; ECG, electrocardiogram; GP, general practitioner; NR, not reported; NVAF, non-valvular atrial fibrillation; SD, standard deviation; SPORTIF, Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation.

a Dose or INR of the respective therapy not reported in the study.

b Longitudinal follow-up of patients from the randomised NASPEAF cohort,[39] along with new admissions. There might be a significant overlap of populations in the two studies.

c All patients with ST-segment elevation MI and undergoing PCI.

d Either warfarin or acenocoumarol.

e Previous stroke/TIA/SE, hypertension, left ventricular dysfunction (ejection fraction <40% or symptomatic systolic or diastolic HF), aged ≥75 years or aged ≥65 years with known coronary disease/diabetes mellitus.

f Hypertension requiring medical treatment, diabetes mellitus (type 1 or 2), symptomatic HF or left ventricular dysfunction (ejection fraction <40%), previous stroke or TIA, aged >75 years).

g Name of the therapy not reported.

h All patients had AF and AMI.

i Secondary analysis excluding patients lost to follow-up.

j Presence of at least one of the following: impaired left ventricular dysfunction [evidenced by recent (≤100 days) congestive HF, or fractional shortening ≤25% by M-mode echocardiography; systolic blood pressure of >160 mmHg at study entry] prior ischaemic stroke, TIA or SE (i.e. prior TE); female sex or aged >75 years.

Studies which were used for data extraction and outcomes reported in subsequent sections. others have not been reported separately if they did not provide additional information to existing randomised data. Where required, original papers were used to extract methodological information for post-hoc or subgroup analysis publications.

TABLE 7 Quality assessment of studies reporting non-randomised comparisons

Study, total no., mean follow-up (SD)	Method of outcome measurement	Blinding of assessors	Outcome definitions clearly explained?	Indications of APT in the study	Time of APT employment	Which parts of the study were prospective?[a]	Comments
Hansen *et al.*, 2010, $n = 118{,}606$, 3.3 (2.6) years[63]	Events identified from registry through ICD-10 coded diagnoses[b]	Yes	Yes	Physician's discretion	Unclear	All stages retrospective	Previous warfarin/aspirin/clopidogrel treatment: 12.8%/16.7%/1.0%, respectively
Bover *et al.*, 2009, $n = 574$, 4.2 years[54]	Hospital follow-up and INR measurement in laboratories	No	Yes	Physician's discretion or patient preference	During follow-up	All stages prospective	70% of patients recruited from NASPEAF cohort; patients on combined therapy reported at a higher risk of stroke[c]
Lopes *et al.*, 2009, $n = 276$, 90 days[50]	Telephone contact at 30 and 90 days	Unclear	Yes	NR	At discharge	All stages prospective	Analysis of patients enrolled in another trial[91] to compare outcomes in patients with new-onset AF vs those diagnosed with AF at discharge
Abdelhafiz and Wheeldon, 2008, $n = 402$, 19 months[51]	Telephone interview every 4–6 weeks with medical notes review	Yes	Yes	Physician's discretion and presence of IHD	NR	All stages prospective	
Amadeus Investigators, 2008, $n = 4576$, 339 days[72]	Follow-up at week 1, 2, 6, 13 and every 3 months thereafter, or when event occurred	Yes	Yes	Physician's discretion	Unclear	All stages prospective	Trial stopped after randomisation because of excessive bleeding in patients on idraparinux; 76% of patients reported on VKA before entry into trial
Ezekowitz *et al.*, 2007 (RCT – PETRO), $n = 502$, 22 weeks[73]	Outpatient follow-up at 1, 2, 4, 8, and 12 weeks after randomisation (to dabigatran or warfarin)	Yes	Yes	NR	During the study	All stages prospective	After entry of approximately half of the patients, the requirement for CAD was removed to facilitate recruitment; all patients treated with VKA for ≥ 8 weeks prior to inclusion

continued

TABLE 7 Quality assessment of studies reporting non-randomised comparisons (*continued*)

Study, total no., mean follow-up (SD)	Method of outcome measurement	Blinding of assessors	Outcome definitions clearly explained?	Indications of APT in the study	Time of APT employment	Which parts of the study were prospective?[a]	Comments
Suzuki *et al.*, 2007, $n = 667$, 1 year[56]	Database review	Yes	Yes	Other cardiovascular diseases	Unclear	All stages retrospective	Study conducted on Japanese AF patients attending a hospital for cardiovascular diseases
Burton *et al.*, 2006, $n = 601$, 42 months[57]	Record review and patient contact through letters	Yes	Yes	Physician's discretion	Any time during follow-up	All stages retrospective	
Stenestrand *et al.*, 2005, $n = 5616$, 1–8 years[58]	Review of hospital records	Yes	No	Physician's discretion	At discharge	All stages retrospective	Name of OAC not specified in the study, 18% on ACT before admission
Flaker *et al.*, 2006; $n = 7304$, 16.6 months[69]	Stroke assessment every 6 months and after an event	Yes	Yes	Age ≥65 years with CAD with or without diabetes mellitus	Unclear	All stages prospective	Significant baseline differences in those receiving ACT + APT and ACT alone; 73.4% received anticoagulation and 20.7% were taking aspirin prior to study entry
Johnson *et al.*, 2005, $n = 228$, 28 months[59]	Patient contacted on telephone and questionnaires when event occurred[d]	Yes	Yes	NR	NR	All prospective	44.3% on warfarin ($n = 101/228$) for varying lengths of time before their index admission
Blich *et al.*, 2004, $n = 506$, 7.2 years[61]	Review of patient records and interview with patient's GP	Yes	No	Physician's discretion	At diagnosis, during follow-up, or before TE event	All stages retrospective	26.9% of patients receiving warfarin at diagnosis, 6.5% were young or had no stroke risk factors
Shireman *et al.*, 2004, $n = 10{,}093$, 180 days[60]	Review of Medicare hospital claims for events with ICD-9-CM coding	Yes	Yes	Presence of CHD	After discharge	All stages retrospective	

Study, total no., mean follow-up (SD)	Method of outcome measurement	Blinding of assessors	Outcome definitions clearly explained?	Indications of APT in the study	Time of APT employment	Which parts of the study were prospective?[a]	Comments
Klein *et al.*, 2003, RCT – ACUTE cohort, $n = 1222$, 8 weeks[62]	Weekly INR testing and TEE at 4 weeks	Unclear	Yes	NR	At enrolment	All stages prospective	No. of patients on ACT or ACT + APT not reported No indication if patients took aspirin throughout the study period
Hart *et al.*, 2000, $n = 2012$, 2 years[55]	Clinic follow-up every 3–6 months	unclear	Yes	Randomised[e]	During follow-up	All stages prospective	Incomplete information on only a few patients on combined therapy and ACT alone reported from authors of the randomised study[43]
Toda *et al.*, 1998; $n = 288$, 7.2 years[52]	Review of patient records, or patient questionnaires, supplemented with GP contact Cranial CT scan and/or angiography used to assess outcomes	Yes	Yes	Physician's discretion	At baseline and before event	Outcome assessment	Study conducted on hospitalised Japanese patients with AF aged 8–82 years
Albers *et al.*,1996; $n = 309$[53]	Chart reviews performed by HCPs in consultation with physician	Yes	No	Physician's discretion	Admission and discharge	Outcome assessment – prospective	18% had no risk factors for stroke and 44% had contraindications for ACT on admission 23.6% took warfarin before admission 77% white population

ACUTE, Assessment of Cardioversion Using Transesophageal Echocardiography; CT, computerised tomography; GP, general practitioner; HCP, health-care professionals (pharmacists and nurses); ICD-9-CM, International Classification Of Diseases, Ninth Edition, Clinical Modification; ICD-10, International Classification Of Diseases, Tenth Edition; IHD, ischaemic heart disease; NR, not reported; OAC, oral anticoagulant; SD, standard deviation; TEE, transoesophageal echocardiography.

a Stages: identification of participants, assessment of baseline and allocation to treatment, outcome assessment.

b Bleeding and stroke events identified through ICD-10 codes in the registry, deaths register used for mortality outcome.

c Patients on acenocoumarol plus aspirin had more risk factors for embolism compared with all other groups, patients on acenocoumarol plus triflusal (300 mg or 600 mg) had more risk factors for stroke compared with those on acenocoumarol alone.

d Information supplied by patients was corroborated by hospital medical records, GPs, specialists, and pathology services (and relatives).

e Non-randomised follow-up of patients from the randomised SPAF III cohort.[43]

Outcomes

Not all of the studies measured or reported information for the primary and secondary outcomes of the review.

Table 8 details the outcomes reported in each study. Not surprisingly, bleeding, stroke and/or mortality-related outcomes were the most frequently reported. The time in therapeutic INR range was infrequently measured. To some extent this might be due to the nature of the anticoagulant agents used in some studies and thus the absence of a need for this outcome. Patient quality of life, in-stent thrombosis and revascularisation procedures were not reported in any of the studies.

Methodological issues

Twenty-three studies in 35 articles[39–73] reported the outcomes of interest for combined anticoagulant plus APT compared with ACT alone in patients with AF. Of these, 5 studies in 11 articles[39–49] reported randomised comparisons, whereas 18 studies in 24 articles[50–73] reported non-randomised comparisons. The characteristics of these studies have been reported previously in *Tables 4* and *6*.

Not all of the included studies provided non-randomised data that added information to the robust randomised data. Data were extracted from these studies, but not reported in this review. Reasons for non-inclusion of study data from such studies have been reported in *Appendix 7*. A few studies did not report the number of events[50,56,62,68,70,72] or did not clearly report the number of participants in each therapy group,[57,58,61,64,65] whereas a few other publications reported duplicate data from included primary studies.[44–47,49,71] A few studies reported non-randomised data that did not add any new information to the data available from other studies, either because of a very small sample size[51] or because they did not specify the name of the APT in the combination anticoagulation plus antiplatelet arm.[52,59] Other studies that furnished complete and tangible data were included.

An example of such studies are the Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) studies.[64–71] The original articles of SPORTIF III[64] and SPORTIF V[65] did not specify the number of events and number of participants in the interventions of interest (anticoagulant plus antiplatelet and anticoagulant alone). Six articles[66–71] reported pooled post hoc analyses of these two studies.[64,65] Of these, two pooled analyses, by White *et al*.,[68] and Douketis *et al*.,[70] did not report data on the number of events or the number of participants for either intervention group; however, this information was reported in pooled analyses by Flaker *et al*.[69] and Akins *et al*.[67] Two other publications[66,71] reported data for stroke, or stroke and bleeding outcomes, which were also reported in pooled analyses.[67,69] Flaker *et al*.[69] reported data on bleeding, mortality, stroke, and combined stroke and SE events, with detailed information on the number of events and participants in the SPORTIF cohorts. Therefore, this pooled analysis was reported in the review. Akins *et al*.[67] furnished data for bleeding, stroke and SE events specifically for patients with previous embolic events in the SPORTIF trials. Therefore, this study consisting of a population who were at a high risk of stroke was reported in the review.

Primary outcomes of the review

Outcome 1: stroke

Thirteen articles yielded outcome data for stroke.[42–45,47–50,54,55,63,66,69] Of these, three studies in seven articles[42–45,47–49] reported randomised comparisons. The findings of these are reported in *Table 9*. The remaining five articles[50,54,55,63,66,69] reported non-randomised comparisons, of which four were primary studies,[50,54,55,63] and two were secondary analyses[66,69] of the SPORTIF III and SPORTIF V studies. *Table 10* presents the findings of these studies.

TABLE 8 Outcomes reported in the included studies

Author, year (name of study)	Outcomes												
	Primary outcome measures							Secondary outcome measures					
	Stroke–any[a]	TIA	SE	Stroke + SE[a]	AMI	In-stent thrombosis	Death – vascular	Death – all cause	Bleeding	Quality of life	Adverse events[b]	Revascularisation procedures (e.g. PCI)	Percentage time in INR range
Randomised comparisons[c]													
Pérez-Gómez et al., 2004 (RCT – NASPEAF)[39]	✓	✓	✓	✓	✓		✓		✓				✓
Pérez-Gómez et al., *2007 (RCT – NASPEAF)*[44]	✓		✓				✓		✓				
Pérez-Gómez et al., *2006 (RCT – NASPEAF)*[45]	✓	✓	✓				✓		✓				
Pérez-Gómez et al., *2006 (RCT – NASPEAF)*[46]									✓				
Lidell *et al.*, 2003,[40]									✓				✓
Lechat *et al.*, 2001 (RCT – FFAACS)[41]			✓				✓	✓					
Gullov *et al.*, 1998, (RCT – AFASAK II)[42]	✓	✓	✓	✓	✓		✓	✓	✓				✓
Gullov et al., 1999, *(RCT – AFASAK II review)*[47]	✓	✓	✓	✓	✓		✓	✓	✓				✓
SPAF investigators, 1996, (RCT – SPAF III)[43]	✓	✓	✓	✓	✓		✓	✓	✓				✓
Hart et al., *2000 (SPAF I, II, III pooled)*[48]	✓												
Blackshear et al., *1999 (RCT – SPAF-III)*[49]													

continued

TABLE 8 Outcomes reported in the included studies (*continued*)

Author, year (name of study)	Outcomes												
	Primary outcome measures							Secondary outcome measures					
	Stroke–any[a]	TIA	SE	Stroke + SE[a]	AMI	In-stent thrombosis	Death – vascular	Death – all cause	Bleeding	Quality of life	Adverse events[b]	Revascularisation procedures (e.g. PCI)	Percentage time in INR range
Non-randomised comparisons													
[d]Hansen *et al.*, 2010[63]	✓								✓				
[d,e]Bover *et al.*, 2009[54]	✓		✓	✓	✓			✓	✓				✓
Lopes *et al.*, 2009[50]	✓												
Abdelhafiz and Wheeldon, 2008[51]									✓				
Amadeus Investigators, 2008[72]									✓				
[d]Ezekowitz *et al.*, 2007 (RCT – PETRO)[73]			✓						✓				
Suzuki *et al.*, 2007[56]									✓				
Burton *et al.*, 2006[57]									✓				
Stenestrand *et al.*, 2005[58]								✓					
SPORTIF V investigators, 2005[65]									✓				
SPORTIF III Investigators, 2003[64]									✓				
Teitelbaum et al., *2008*[66]	✓								✓				
[d]*Akins* et al., *2007*[6]				✓					✓				

Author, year (name of study)	Outcomes												
	Primary outcome measures							Secondary outcome measures					
	Stroke–any[a]	TIA	SE	Stroke + SE[a]	AMI	In-stent thrombosis	Death – vascular	Death – all cause	Bleeding	Quality of life	Adverse events[b]	Revascularisation procedures (e.g. PCI)	Percentage time in INR range
White HD et al., *2007*[68]				✓	✓			✓	✓				
Halperin, 2005[71]				✓									
[d]*Flaker* et al., *2006*[69]	✓			✓				✓	✓				
Douketis et al., *2006*[70]									✓				
Johnson *et al.*, 2005[59]									✓				
Blich *et al.*, 2004[61]			✓						✓				
Shireman *et al.*, 2004[60]									✓				
Klein *et al.*, 2003[62]									✓				
[f]Hart *et al.*, 2000[55]	✓												
Toda *et al.*, 1998[52]			✓										
Albers *et al.*, 1996[53]									✓				

a Non-fatal, fatal, ischaemic, haemorrhagic, disabling or minor.
b Composite of all-cause mortality, non-fatal MI and stroke.
c Original publication reporting the RCT used for reporting data in subsequent outcome sections.
d Data from only these studies reported in the outcomes section.
e Longitudinal follow-up of NASPEAF trial,[39] with additional newly enrolled patients.
f Longitudinal follow-up of SPAF trials.[43]

Note
Italic text denotes subgroup analyses of preceding original papers.

The study by Hansen *et al*.[63] reported stroke outcomes for a large number of patients with AF (118,606) over a long follow-up (3.3 years); however, neither the number of stroke events nor the details of the antiplatelet and ACT were reported. Therefore, this study is not reported in this section. Of the studies that reported non-randomised comparisons, Lopes *et al*.,[50] Teitelbaum *et al*.[66] and Hart *et al*.[55] are not mentioned further in this section. The reasons for these have been reported in *Appendix 7*. The characteristics of these studies have been reported previously (see *Table 6*).

Stroke events were reported either on their own (stroke alone) or in conjunction with other events such as embolism or bleeding in the included studies. In those studies that reported stroke alone, strokes were frequently classified as non-fatal, fatal, haemorrhagic, ischaemic or disabling. A precise definition of these groupings or subclassifications of stroke was not always supplied in the study reports and/or the definitions may have varied between studies for the same subclassification.

The findings of the included studies for each of these composite and/or subclassifications of stroke are detailed below.

Stroke: all

One randomised comparison[42] and two non-randomised comparisons[54,69] compared a VKA plus aspirin, to a VKA alone. The pooled analysis of the SPORTIF III and V trials[69] and the longitudinal follow-up study by Bover *et al*.,[54] add data to the randomised comparisons on the risk of stroke for patients receiving VKA plus aspirin compared with VKA alone.

The AFASAK II study[42] and the pooled analysis of SPORTIF trials by Flaker *et al*.[69] defined stroke as an acute onset of focal neurological deficit lasting ≥24 hours. Bover *et al*.[54] did not report a precise a definition of stroke in their study.

The AFASAK II[42] study compared combined fixed-dose warfarin (1.25 mg) plus aspirin (300 mg daily), with either adjusted-dose warfarin (target INR 2.0–3.0) alone or with fixed-dose warfarin (1.25 mg daily) alone. The findings of this study[42] have been reported in *Table 9*. The risk profile of the patients enrolled in this study was not specified. There were no significant differences in the rate of stroke between patients receiving the combination of fixed-dose warfarin and aspirin, and either those receiving fixed-dose warfarin alone [11/171 (6.4%) vs 13/167 (7.8%), respectively] with a RR of 0.83 (95% CI 0.38 to 1.79), or those receiving adjusted-dose warfarin alone [11/171 (6.4%) vs 10/170 (5.9%), respectively], RR 1.09 (95% CI 0.48 to 2.51), over a mean follow-up period of 3.5 years.[42]

The pooled analysis of the SPORTIF studies by Flaker *et al*.[69] compared adjusted-dose warfarin (INR 2.0–3.0) plus aspirin (100 mg) with adjusted-dose warfarin (INR 2.0–3.0) alone, over a mean follow-up period of 16.5 months. The rate of stroke was similar in patients in the combined therapy group compared with those on adjusted-dose warfarin (INR 2.0–3.0 alone) [11/481 (2.3%) vs 67/3172 (2.1%)], respectively. The rate of stroke was much higher in the AFASAK II study[42] for patients receiving combination fixed-dose warfarin plus aspirin than for those with adjusted-dose warfarin plus aspirin in the SPORTIF studies;[69] 11 out of 171 (6.4%) compared with 11 out of 481 (2.3%), respectively. The stroke rate was also much higher in patients receiving either adjusted-dose, 10 out of 170 (5.9%) or fixed-dose, 13 out of 167 (7.8%) warfarin alone in the AFASAK II[42] study than for those receiving adjusted-dose warfarin alone in the SPORTIF studies,[69] 67 out of 3172 (2.1%).

Bover *et al*.[54] compared adjusted-dose acenocoumarol (INR target 1.9–2.5) plus aspirin (100 mg) with adjusted-dose acenocoumarol (INR 2.0–3.0) alone, over a mean follow-up period of 4.92 years. The combination of acenocoumarol with aspirin demonstrated fewer stroke events [1/34 (2.9%)] than with acenocoumarol alone [15/265 (5.7%)].

Bover *et al*.[54] also compared combination adjusted-dose acenocoumarol (INR 1.9–2.5) plus two different regimes of triflusal (600 and 300 mg) with adjusted-dose acenocoumarol (INR 2.0–3.0) alone. Fewer strokes were observed with the combination of acenocoumarol plus triflusal 600 mg than for

TABLE 9 Stroke outcomes reported in studies with randomised comparisons

Author, year, study name	Stroke risk, follow-up (mean)	ACT + APT, *n*	No. of events/participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)	RR (95% CI)
[a]Pérez-Gómez *et al.*, 2004, RCT – NASPEAF [39]	High risk,[b] 2.95 years	Adjusted-dose acenocoumarol (1.4–2.4) + triflusal (600 mg), *n* = 223	Non-fatal: 6/223 (2.7)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 247	Non-fatal: 6/247 (2.4)	1.11 (0.36 to 3.38)
	Intermediate risk,[c] 2.6 years[d]	Adjusted-dose acenocoumarol (1.25–2.0) + triflusal (600 mg), *n* = 222	Non-fatal: 3/222 (1.4)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 232	Non-fatal: 3/232 (1.3)	1.05 (0.21 to 5.12)
[e]Gullov *et al.*, 1998 RCT – AFASAK II [42]	Risk NR, 3.5 years	Fixed-dose warfarin (1.25 mg) + aspirin (300 mg), *n* = 171	All: 11/171 (6.4)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 170	All: 10/170 (5.9)	1.09 (0.48 to 2.51)
			Non-infarct: 3/171 (1.8)		Non-infarct: 3/170 (1.8)	0.99 (0.20 to 4.86)
			Minor: 4/171 (2.3)		Minor: 0/170 (0)	8.95 (0.49 to 164.92)
			Disabling: 4/171 (2.3)		Disabling: 3/170 (1.8)	1.33 (0.30 to 5.83)
			Fatal: 0/171 (0)		Fatal: 0/170 (0)	Not estimable
			Haemorrhagic: 0/171 (0)		Haemorrhagic: 1/170 (0.6)	0.33 (0.01 to 8.08)
			Ischaemic: 8/171 (4.7)		Ischaemic: 3/170 (1.8)	2.65 (0.72 to 9.82)
			Non disabling: 3/171 (1.8)		Non-disabling: 4/170 (2.4)	0.75 (0.17 to 3.28)
				Fixed-dose warfarin (1.25 mg), *n* = 167	All: 13/167 (7.8)	0.83 (0.38 to 1.79)
					Non infarct: 6/167 (3.6)	0.49 (0.12 to 1.92)
					Minor: 3/167 (1.8)	1.30 (0.30 to 5.73)
					Disabling: 2/167 (1.2)	1.95 (0.36 to 10.52)
					Fatal: 2/167 (1.2)	0.20 (0.01 to 4.04)
					Haemorrhagic: 0/167 (0)	Not estimable
					Ischaemic: 5/167 (2.9)	1.56 (0.52 to 4.68)
					Non-disabling: 4/167 (2.4)	0.73 (0.17 to 3.22)

continued

TABLE 9 Stroke outcomes reported in studies with randomised comparisons (*continued*)

Author, year, study name	Stroke risk, follow-up (mean)	ACT + APT, *n*	No. of events/participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)	RR (95% CI)
[f]SPAF investigators to 1996 RCT – SPAF[43]	High risk,[g] 1.1 years	Adjusted-dose warfarin (INR 1.2–1.5) + aspirin (325 mg), *n* = 521	Disabling:[d] 31/521 (5.9) Ischaemic: 43/521 (8.3) Ischaemic – fatal: 5/521 (0.9)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 523	Disabling:[d] 10/523 (1.9) Ischaemic: 11/523 (2.1) Ischaemic – fatal: 1/523 (0.2)	2.83 (1.44 to 5.57) 3.92 (2.05 to 7.52) 5.02 (0.59 to 42.81)

NR, not reported; NVAF, non-valvular atrial fibrillation.

a Supported by *n* = 2 subgroup analyses[44,45] that reported duplicate data and are not reported in this table.

b Either NVAF with prior embolism or those with mitral stenosis, with and without prior embolism.

c NVAF with no embolism at baseline.

d Includes all fatal strokes, ischaemic strokes and haemorrhagic strokes.

e Supported by an analysis[47] that reported duplicate data; not reported in this table.

f Supported by one subgroup analysis[48] that did not report additional data; not reported in this table.

g Presence of at least one: impaired left ventricular function manifested by recent (≤100 days) congestive heart disease or fractional shortening ≤25% by M-mode echocardiography; systolic blood pressure of > 160 mmHg at study entry; prior ischaemic stroke, TIA or SE (i.e. prior TE); female sex; and aged >75 years.

TABLE 10 Stroke outcome: studies reporting non-randomised comparisons

Author, year	Stroke risk, follow-up	ACT + APT, *n*	No. of events/total participants in ACT + APT group (%)	ACT (alone), *n*	No. of events/total participants in ACT group (%)
[a]Bover *et al.*, 2009[54]	Risk NR, 4.92 years	Adjusted-dose acenocoumarol (1.9–2.5) + triflusal (600 mg), *n* = 155	All:[b] 5/155 (3.2) Haemorrhagic:1/155 (0.6) Lethal: 2/155 (1.3)	Adjusted-dose acenocoumarol (2.0–3.0), *n* = 265	All:[b] 15/265 (5.7) Haemorrhagic: 5/265 (1.9) Lethal: 4/265 (1.5)
		Adjusted-dose acenocoumarol (1.9–2.5) + triflusal (300 mg), *n* = 121	All:[b] 8/120 (6.7) Haemorrhagic: 0/120 (0) Lethal: 3/120 (2.5)		
		Adjusted-dose acenocoumarol (1.9–2.5) + aspirin (100 mg), *n* = 34	All:[b] 1/34 (2.9) Haemorrhagic: 1/34 (2.9) Lethal: 1/34 (2.9)		
[c]Flaker *et al.*, 2006[69]	High risk,[d] 16.5 months	Adjusted-dose warfarin (2.0–3.0) + aspirin (≤100 mg), *n* = 481	All: 11/481 (2.3)	Adjusted-dose warfarin (2.0–3.0), *n* = 3172	All: 67/3172 (2.1)
		Ximelagatran (36 mg b.i.d.) + aspirin (≤100 mg), *n* = 531	All: 11/531 (2.1)	Ximelagatran (36 mg b.i.d.), *n* = 3120	All: 50/3120 (1.6)

b.i.d., dose administered twice daily; NR, not reported.

a Longitudinal follow-up of randomised cohort of NASPEAF study[39] with additional participants.

b Includes ischaemic, fatal and haemorrhagic stroke.

c Pooled analysis of SPORTIF III and SPORTIF V trials with duplicate data on stroke reported in another pooled analysis[66] not reported in this table.

d Previous stroke/TIA/SE, hypertension, left ventricular dysfunction (ejection fraction <40% or symptomatic systolic or diastolic HF), age ≥75 years or age ≥65 years with known coronary disease/diabetes mellitus.

acenocoumarol alone, 5 out of 155 (3.2%) compared with 15 out of 265 (5.7%), respectively. However, stroke rates were higher in those receiving acenocoumarol plus triflusal 300 mg than in those receiving with acenocoumarol alone, 8 out of 120 (6.7%) and with 15 out of 265 (5.7%), respectively. However, there were population complexities in this non-randomised study (see *Between-study differences*, above).

The pooled analysis of the SPORTIF trials by Flaker *et al*.[69] also compared ximelagatran (36 mg twice daily) plus additional aspirin (100 mg) with ximelagatran (36 mg) alone, over a mean follow-up period of 16.5 months. A higher rate of stroke was observed in patients on combined therapy group than in those on ximelagatran alone [11/531 (2.1%) vs 50/3120 (1.6%), respectively]. However, it is to be noted that aspirin use was based on clinical need and, thus, the comparison may be confounded by indication.[65,68]

Summary

Overall, there were few stroke events reported and there is conflicting evidence regarding the benefit of anticoagulation plus APT over anticoagulation alone in the reduction of all stroke events, with two studies[42,69] (one randomised[42] and one non-randomised[69]) reporting no differences, whereas another non-randomised study[54] reports equivocal data, demonstrating fewer strokes with two combination regimes of ACT plus APT over ACT alone [with acenocoumarol plus aspirin (although only 34 patients received this combination) and acenocoumarol plus triflusal 600 mg] but more strokes with acenocoumarol plus triflusal 300 mg.[54]

Fatal stroke

The AFASAK II[42] and SPAF III[43] studies reported randomised comparisons for the outcome of fatal stroke comparing different regimes of combined warfarin plus aspirin, with warfarin alone, whereas Bover *et al*.,[54] reported non-randomised data comparing acenocoumarol plus aspirin with acenocoumarol alone. The findings of these studies are reported in *Tables 9* and *10*, respectively.

In both studies reporting randomised comparisons (AFASAK II[42] and SPAF III[43]), stroke was defined as a focal neurological deficit of presumed vascular genesis lasting more than 24 hours, where stroke assessment was undertaken using neuroimaging. However, Bover *et al*.[54] did not report a precise definition of stroke in their study.

The AFASAK II study[42] compared fixed-dose warfarin (1.25 mg) plus aspirin (300 mg daily), with either adjusted-dose warfarin (target INR 2.0–3.0) alone or with fixed-dose warfarin (1.25 mg daily) alone (see *Table 9*). The risk profile of the patients enrolled in this study was not specified. No fatal strokes were reported among patients receiving either combined warfarin and aspirin or those receiving warfarin alone. However, two fatal strokes were reported in patients receiving fixed-dose warfarin alone [2/167 (1.2%) vs 0/171 (0%), respectively, RR 0.20 (95% CI 0.01 to 4.04)] over a mean follow-up period of 3.5 years.[42]

The SPAF III study[43] compared adjusted-dose warfarin (INR 1.2–1.5) plus aspirin (325 mg) with adjusted-dose warfarin (target INR 2.0–3.0) alone in high-risk patients with AF. A non-significant but higher incidence of fatal stroke was observed in the combined therapy arm than in those treated with warfarin alone [5/521 (0.9%) vs 1/523 (0.2%), respectively, RR 5.02 (95% CI 0.59 to 42.81)] over a mean follow-up period of 1.1 years.[43]

Only eight fatal strokes occurred in these two RCTs. Among those receiving combined therapy, the rate of fatal stroke was 0.9% (5/521) in the SPAF III[43] study compared with 0% (0/171) in the AFASAK II study.[42] The rate of fatal stroke was similar but numerically higher among those receiving adjusted-dose

warfarin alone in the SPAF III study,[43] 1/523 (0.2%), than 0/170 (0%) in the AFASAK II study,[42] and higher among those receiving fixed-dose warfarin alone in the AFASAK II[42] study [2/167 (1.2%) vs 1/523 (0.2%), respectively].

Bover *et al*.[54] reported a non-randomised comparison for the incidence of fatal stroke comparing adjusted-dose acenocoumarol (INR 1.9–2.5) plus an antiplatelet in three different regimes (triflusal 600 mg, triflusal 300 mg and aspirin 100 mg) with adjusted-dose acenocoumarol (INR 2.0–3.0) alone. The combination of acenocoumarol plus aspirin and acenocoumarol plus triflusal 300 mg demonstrated a higher proportion of fatal strokes than acenocoumarol alone [1/34 (2.9%), 3/120 (2.5%) vs 4/265 (1.5%), respectively] during a mean follow-up of 4.92 years. Rates of fatal stroke were similar among those receiving combination acenocoumarol plus triflusal 600 mg and acenocoumarol alone [2/155 (1.3%) vs 4/265 (1.5%), respectively].

Summary

Very few fatal stroke events were reported. Two randomised studies[42,43] found no significant reduction in the risk of fatal stroke with ACT plus APT over ACT alone. One non-randomised study[54] also reported no benefit of combination therapy over anticoagulation alone in lowering the risk of fatal stroke.

Non-fatal stroke

One study (NASPEAF[39]) reported a randomised comparison for non-fatal stroke comparing adjusted-dose acenocoumarol (INR 1.4–2.4) plus triflusal (600 mg) with acenocoumarol alone (INR 2.0–3.0) in high-risk patients, and a combination of adjusted-dose acenocoumarol (INR 1.2–2.0) plus additional triflusal (600 mg) with acenocoumarol alone (INR 2.0–3.0) in intermediate-risk patients. *Table 9* presents the findings of this study. Stroke was defined as a focal neurological deficit lasting more than 24 hours, where neuroimaging was used to define the ischaemic or intracranial aetiology.[39]

Similar rates of non-fatal stroke occurred with combination therapy and anticoagulation alone in the high-risk patients [6/223 (2.7%) vs 6/247 (2.4%), respectively], RR 1.11 (0.36–3.38), during a median follow-up of 2.95 years. Analogous rates were observed in the intermediate-risk group in both the combination therapy and anticoagulation alone group [3/222 (1.4%) vs 3/232 (1.3%), respectively], RR 1.05 (95% CI 0.21 to 5.12), after a median follow-up of 2.6 years.

There was no non-randomised evidence identified for non-fatal stroke.

Summary

Combination therapy did not decrease the risk of non-fatal stroke compared with anticoagulation alone in one randomised study.[39]

Haemorrhagic stroke

The AFASAK II study[42] reported randomised data, and Bover *et al*.[54] reported a non-randomised comparison for the outcome of haemorrhagic stroke.

The AFASAK II study[42] compared fixed-dose warfarin (1.25 mg) plus aspirin (300 mg) with fixed-dose warfarin (1.25 mg) or adjusted-dose warfarin (INR 2.0–3.0) alone. The risk profile of the patients enrolled in this study was not specified. No haemorrhagic strokes were reported in either those patients on combination therapy or in those receiving fixed-dose warfarin alone, over a mean follow-up period of 3.5 years. One haemorrhagic stroke occurred in a patient receiving adjusted-dose warfarin [1/170 (0.6%); RR 0.33 (95% CI 0.01 to 8.08)[42] compared with combination therapy] (see *Table 9*).

Bover *et al*.[54] compared adjusted-dose acenocoumarol (INR 1.9–2.5) plus an antiplatelet in three different regimes (triflusal 600 mg, triflusal 300 mg, aspirin 100 mg) with adjusted-dose acenocoumarol (INR 2.0–3.0) alone, over a mean follow-up period of 4.92 years.

Fewer haemorrhagic strokes were observed in patients in all three combination therapy arms (triflusal 600 mg, triflusal 300 mg, aspirin 100 mg) than in those patients receiving acenocoumarol alone, 1/155 (0.6%), 0/120 (0%), 1/34 (2.9%) versus 5/265 (1.9%), respectively.[54]

Summary

Only a few haemorrhagic strokes were reported and the available evidence suggests that there is not an increased risk of haemorrhagic stroke with combination ACT plus APT over ACT alone in one randomised study[42] and one non-randomised study.[54]

Ischaemic stroke

The AFASAK II[42] and SPAF III[43] studies reported randomised comparisons for the outcome of ischaemic stroke. The findings of these studies have been reported in *Table 9*. There was no non-randomised evidence available for the outcome of ischaemic stroke.

The AFASAK II study,[42] comparing fixed-dose warfarin (1.25 mg) plus aspirin (300 mg) with adjusted-dose (INR 2.0–3.0) or fixed-dose (1.25 mg) warfarin alone, reported a non-significant but higher incidence of ischaemic stroke in the combined therapy arm [8/171 (4.7%) compared with either adjusted dose 3/170 (1.8%), RR 2.65 (95% CI 0.72 to 9.82)] or fixed-dose [5/167 (2.9%); RR 1.56 (95% CI 0.52 to 4.68)] warfarin alone. The SPAF III study[43] reported significantly higher rates of ischaemic stroke in the combined therapy arm [adjusted-dose warfarin (INR 1.2–1.5) plus aspirin 325 mg) than in those with adjusted-dose warfarin (INR 2.0–3.0) alone [43/521 (8.3%) vs 11/523 (2.1%), respectively, RR 3.92 (95% CI 2.05 to 7.52)] in high-risk patients with AF over a mean follow-up period of 1.1 years.

The rate of ischaemic stroke varied between these two RCTs.[42,43] In patients receiving combination therapy, the risk of ischaemic stroke was much higher in the SPAF III[43] study than in the AFASAK II[42] study [43/521 (8.3%) vs 8/171 (4.7%), respectively]. Among those receiving dose-adjusted warfarin (INR 2.0–3.0), the rate of ischaemic stroke was similar in both SPAF III[43] and AFASAK II studies[42] [11/523 (2.1%) vs 3/170 (1.8%), respectively]. The rate of ischaemic stroke was higher in those receiving fixed-dose warfarin in the AFASAK II[42] study than in those receiving dose-adjusted warfarin in either AFASAK II[42] or SPAF III[43] study [5/167 (2.9%) vs 3/170 (1.8%), 11/523 (2.1%), respectively]. The differences in the rates may reflect the heterogeneity between the included studies (see *Between-study differences*).

Summary

There is conflicting evidence regarding the benefit of combination ACT plus APT compared with ACT alone in the reduction of ischaemic stroke, with one randomised study[42] demonstrating no significant difference, whereas another randomised study[43] suggests a significantly increased risk of ischaemic stroke with combination therapy.

Disabling stroke

The AFASAK II[42] and SPAF III[43] studies reported randomised comparisons for the outcome of disabling stroke. The findings of these studies are reported in *Table 9*. There was no non-randomised evidence available for this outcome.

The SPAF III study[43] defined disabling stroke as stroke that was graded ≥2 on the modified Rankin scoring system, whereas the AFASAK II study[42] did not specify a definition for disabling stroke.

The AFASAK II study[42] reported a non-significant but higher incidence of disabling stroke in the combined therapy arm [fixed-dose (1.25 mg) warfarin plus aspirin 300 mg] than in either adjusted-dose warfarin (target INR 2.0–3.0) alone [4/171 (2.3%) vs 3/170 (1.8%), respectively, RR 1.33 (95% CI 0.30 to 5.83)] or fixed-dose warfarin (1.25 mg) alone [4/171 (2.3%) vs 2/167 (1.2%), respectively] (see *Table 9*) over a mean follow-up period of 3.5 years. The risk profile of the patients enrolled in this study[42] was not specified.

The SPAF III study[43] reported significantly higher rates of disabling stroke in the combined therapy arm [adjusted-dose warfarin (INR 1.2–1.5) plus aspirin 325 mg] than in the adjusted-dose warfarin (INR 2.0–3.0) alone group [31/521 (5.9%) vs 10/523 (1.9%) respectively, RR 2.83 (95% CI 1.44 to 5.57)] in high-risk patients with AF over a mean follow-up period of 1.1 years.[43]

The rate of disabling strokes was much higher in patients receiving combination therapy in the SPAF III[43] study than in the AFASAK II[42] study [31/521 (5.9%) vs 4/171 (2.3%), respectively]. Similar rates of disabling stroke were evident in patients receiving adjusted-dose warfarin alone in both SPAF III[43] and AFASAK II[42] studies [10/523 (1.9%) vs 3/170 (1.8%), respectively], and those receiving fixed-dose warfarin alone in the AFASAK II[42] study [2/167 (1.2%)]. Such differences reflect significant heterogeneity between the included studies (see *Between-study differences*, above).

Summary

There is conflicting evidence regarding the benefit of combination ACT plus APT compared with ACT alone in the reduction of disabling stroke, with one randomised study[42] demonstrating no significant difference, whereas another randomised study[43] suggests a significantly increased risk of disabling stroke with combination therapy.

Other stroke definitions

The AFASAK II study[42] also reported the incidence of minor, non-disabling and non-infarct strokes. The findings of this study are reported in *Table 9*. The definitions of these subclassifications have not been reported in the study.[42] Fixed-dose warfarin (1.25 mg) plus aspirin (300 mg) demonstrated a non-significant but higher risk of minor stroke than with either adjusted-dose warfarin (INR 2.0–3.0) alone [4/171 (2.3%) vs 0/170 (0%), respectively, RR 8.95 (95% CI 0.49 to 164.92)] or fixed-dose warfarin alone [4/171 (2.3%) vs 3/167 (1.8%), respectively, RR 1.30 (95% CI 0.30 to 5.73)].[42]

This study also demonstrated similar rates of non-disabling stroke among those receiving combination therapy [3/171 (1.8%)], adjusted-dose warfarin alone [4/170 (2.4%)] and fixed-dose warfarin alone [4/167 (2.4%)].[42] The rate of non-infarct stroke was the same among those receiving combination therapy and adjusted-dose warfarin alone [3/171 (1.8%) vs 3/170 (1.8%), respectively] but was twice as high in those receiving fixed-dose warfarin alone [6/167 (3.6%)][42] (see *Table 6*).

There was no non-randomised evidence available for these three subclassifications of stroke.

The differences in stroke outcomes reported in the included studies may reflect the methodological differences between these studies discussed above (see *Between-study differences*). In addition, although four studies[39,42,43,69] used the same definition of stroke, one non-randomised study[54] did not provide a specific definition of stroke, and the stroke subtypes reported varied and were not always clearly defined by each study, which may account for variation in the reported event rates. The likelihood of stroke is increased when INR is < 2.0 and, therefore, it is possible that studies using INR targets of < 2.0 in the combination therapy arm may have experienced higher rates of stroke than those using standard INR targets (2.0–3.0), particularly in high-risk populations. Furthermore, only three studies (two randomised[39,43] and one non-randomised[54]) reported TTR for ACT plus APT and ACT alone. TTR is associated with the incidence of stroke events; when TTR is good (≥ 58%), the likelihood of adverse events (ischaemic and haemorrhagic strokes) is reduced.[92] Therefore, differences in the TTR may help to explain differences in the event rates reported.

Outcome 2: transient ischaemic attack

Three studies, reported in five articles[39,42,43,45,47] yielded outcome data for TIA (*Table 11*). Of these, all three reported randomised comparisons,[39,42,43] supported by two subgroup analyses.[45,47] No non-randomised comparisons reported TIA separately as an outcome.

Transient ischaemic attack was similarly defined in the NASPEAF[39] and AFASAK II[42] studies as an acute onset of focal neurological deficit of presumed vascular genesis lasting < 24 hours, regardless of computerised tomography (CT)/magnetic resonance imaging (MRI) findings (AFASAK II) or confirmed by neurological imaging (NASPEAF). The SPAF III[43] study did not define TIA.

Both the AFASAK II[42] and SPAF III[43] studies compared warfarin plus aspirin with warfarin alone, but the warfarin and aspirin regimes differed between the studies.

The AFASAK II[42] study compared fixed-dose warfarin (1.25 mg daily) plus aspirin (300 mg daily) with adjusted-dose warfarin (INR 2.0–3.0) or fixed-dose warfarin (1.25 mg daily). The risk profile of the patients enrolled in this study was not specified. The rate of TIA among patients receiving the combination of warfarin plus aspirin was twice that of patients receiving adjusted-dose warfarin (INR 2.0–3.0) alone [2/171 (1.2%) vs 1/170 (0.6%), respectively, RR 1.99 (95% CI 0.18 to 21.72)] and half that of patients receiving fixed-dose warfarin (1.25 mg daily) alone [2/171 (1.2%) vs 4/167 (2.4%), respectively, RR 0.49 (95% CI 0.09 to 2.63)] over a mean 3.5-year follow-up period.

The SPAF III[43] study compared adjusted-dose warfarin (INR 1.2–1.5) plus aspirin (325 mg daily) with adjusted-dose warfarin (INR 2.0–3.0) alone in high-risk patients with AF. A non-significant but numerically higher number of TIAs were observed in the combined therapy arm than in those receiving adjusted-dose

TABLE 11 Randomised comparisons reporting TIA as an outcome

Author, year, study name	Follow-up	ACT + APT, *n*	No. of events/total participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)	RR (95% CI)
[a]Pérez-Gómez *et al.*, 2004, RCT – NASPEAF[39]	High risk,[b] 2.95 year	Adjusted-dose acenocoumarol (INR 1.4–2.4) + triflusal (600 mg), *n* = 223	TIA: 2/223 (0.9)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 247	TIA: 3/247 (1.2)	0.74 (0.12 to 4.38)
	Intermediate risk,[c] 2.6 years	Adjusted-dose acenocoumarol (INR 1.25–2.0) + triflusal (600 mg), *n* = 222	TIA: 0/222 (0)	Acenocoumarol (2.0–3.0), *n* = 232	TIA: 0/232 (0)	Not estimable
[d]Gullov *et al.*, 1998, RCT – AFASAK II[42]	Risk NR, 3.5 years	Fixed-dose warfarin (1.25 mg) + aspirin (300 mg), *n* = 171	TIA: 2/171 (1.2)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 170	TIA: 1/170 (0.6)	1.99 (0.18 to 21.72)
				Fixed-dose warfarin (1.25 mg), *n* = 167	TIA: 4/167 (2.4)	0.49 (0.09 to 2.63)
SPAF investigators, 1996, RCT – SPAF III[43]	High risk,[e] 1.1 years	Adjusted-dose warfarin (INR 1.2–1.5) + aspirin (325 mg), *n* = 521	TIA: 23/521 (4.4)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 523	TIA: 15/523 (2.9)	1.54 (0.81 to 2.92)

NVAF, non-valvular atrial fibrillation.

a Supported by *n* = 1 subanalysis,[45] which provided duplicate data and are not presented in this table.

b Either NVAF with prior embolism or those with mitral stenosis with or without prior embolism.

c NVAF with no embolism at baseline.

d Supported by *n* = 1 analysis,[47] which provided duplicate data and are not presented in this table.

e Presence of at least one of the following: impaired left ventricular function manifested by recent (≤100 days) congestive HF, or fractional shortening ≤25% by M-mode echocardiography; systolic blood pressure of >160 mmHg at study entry; prior ischaemic stroke, TIA or SE (i.e. prior TE); female sex or aged >75 years.

warfarin alone [23/251 (4.4%) vs 15/523 (2.9%), respectively, RR 1.54 (95% CI 0.81 to 2.92)] over a mean 1.1-year follow-up period.

The TIA event rate was different in these two randomised comparisons. In the combination of adjusted-dose warfarin (INR 1.2–1.5) plus aspirin (325 mg) arm of the SPAF III[43] study, the rate of TIA was 4.4% (23/521) compared with 1.2% (2/171) among those receiving combination fixed-dose warfarin (1.25 mg) plus aspirin (300 mg) in the AFASAK II[42] study. The rate of TIA was also higher in those receiving adjusted-dose warfarin (INR 2.0–3.0) alone in the SPAF III[43] study [15/523 (2.9%)] than in those receiving either adjusted- (INR 2.0–3.0) or fixed-dose warfarin (1.25 mg) alone in the AFASAK II[42] study [1/170 (0.6%) and 4/167 (2.4%), respectively].

The NASPEAF[39] randomised comparison compared adjusted-dose acenocoumarol (INR 1.4–2.4) in combination with triflusal 600 mg with adjusted-dose acenocoumarol (INR 2.0–3.0) alone in high-risk patients and adjusted-dose acenocoumarol (INR 1.2–2.0) and triflusal 600 mg in combination compared with adjusted-dose acenocoumarol (INR 2.0–3.0) alone in intermediate-risk patients.

In the high-risk population, a similar rate of TIA was observed with adjusted-dose acenocoumarol (INR 1.4–2.4) in combination with triflusal 600 mg compared with adjusted-dose acenocoumarol (INR 2.0–3.0) alone [2/223 (0.9%) vs 3/247 (1.2%), respectively, RR 0.74 (95% CI 0.12, 4.38)] after a median follow-up of 2.95 years. No TIAs occurred during the median 2.6 years' follow-up in the intermediate-risk patients.[39]

Two further articles (AFASAK II,[47] NASPEAF[45]) provided subgroup analyses on the AFASAK II[42] and NASPEAF[39] studies; however, these articles simply reported duplicate data from the original studies.

No studies of non-randomised comparisons provided further evidence on TIA.

The differences in TIA outcomes reported in the included studies may reflect the methodological differences between these studies discussed in detail above (see *Between-study differences*).

Summary

The reported incidence of TIAs was low and three randomised studies[39,42,43] found no significant benefit of combination therapy over anticoagulation alone to reduce the risk of TIAs.

Outcome 3: stroke and systemic embolism

Five studies, reported in 10 articles,[39,42–45,47,67–69,71] yielded outcome data for the combination of stroke and SE. Of these, three studies in six articles,[39,42–44,45,47] reported randomised comparisons (*Table 12*). Two studies in four articles[67–69,71] reported pooled analyses of non-randomised comparisons using data from two randomised studies (SPORTIF III and V). The characteristics of the randomised and non-randomised comparison studies have been presented previously in *Tables 4* and *6,* respectively.

A precise definition of stroke was given in all the study reports, but the definitions of stroke that were used varied between the studies. Although the three randomised comparisons[39,42,43] and two pooled analyses of the SPORTIF III and V trials[67,69] defined stroke as an acute onset of focal neurological deficit lasting ≥24 hours, NASPEAF[39] also included TIA, AFASAK II[42] included fatal strokes, SPAF III[43] included only ischaemic strokes, whereas the SPORTIF III and V trials[67,69] included both ischaemic strokes and intracranial haemorrhage (ICH) in their definition. Three studies, NASPEAF,[39] SPAF III[43] and SPORTIF,[67,69] defined SE as an abrupt vascular insufficiency related to arterial occlusion, without previous clinical symptoms

TABLE 12 Randomised comparisons reporting the combined outcome of stroke and systemic embolic events

Author, year, study name	Follow-up	ACT + APT, *n*	No. of events/total participants in ACT + APT arm (%)	ACT [alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)	RR (95% CI)
[a]Pérez-Gómez *et al.*, 2004, RCT – NASPEAF[39]	High risk,[b] 2.95 years	Adjusted-dose acenocoumarol (INR 1.4–2.4) + triflusal (600 mg), *n* = 223	Stroke[c]/any embolism: 12/223 (5.4)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 247	Stroke[c]/any embolism: 20/247 (8.1)	0.66 (0.33 to 1.33)
			Stroke[c]/fatal embolism: 4/223 (1.8)		Stroke[c]/fatal embolism: 8/247 (3.2)	0.55 (0.17 to 1.81)
	Intermediate risk,[d] 2.6 years	Adjusted-dose acenocoumarol (INR 1.25–2.0) + triflusal (600 mg), *n* = 222	Stroke[c]/any embolism: 3/222 (1.4)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 232	Stroke[c]/any embolism: 7/232 (3.0)	0.45 (0.12 to 1.71)
			Stroke[c]/fatal embolism: 0/222 (0)		Stroke[c]/fatal embolism: 3/232 (1.3)	0.15 (0.01 to 2.87)
[e]Gullov *et al.*, 1998 RCT – AFASAK II[42]	Risk NR, 3.5 years	Fixed-dose warfarin (1.25 mg) + aspirin (300 mg), *n* = 171	Stroke[f] + TE:[g] 12/171 (7.0)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 170	Stroke[f] + TE:[g] 12/170 (7.1)	0.99 (0.46 to 2.15)
				Fixed-dose warfarin (1.25 mg), *n* = 167	Stroke[f] + TE:[g] 14/167 (8.4)	0.84 (0.40 to 1.76)
SPAF investigators, 1996, RCT – SPAF III[43]	High risk,[h] 1.1 years	Adjusted-dose warfarin (INR 1.2–1.5) + aspirin (325 mg), *n* = 521	Stroke[i]/SE: 44/521 (8.4)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 523	Stroke[i]/SE: 11/523 (2.1)	4.02 (2.10 to 7.69)

NVAF, non-valvular atrial fibrillation.

a Supported by *n* = 2 subanalyses,[44,45] which provided duplicate data and are not presented in this table.

b Either NVAF with prior embolism or those with mitral stenosis with or without prior embolism.

c Includes TIAs.

d NVAF with no embolism at baseline.

e Supported by *n* = 1 analysis,[47] which provided duplicate data and are not presented in this table.

f Includes fatal stroke.

g For the purposes of this review, SE and TE are classed as same because of broadly similar definitions in the included studies.

h Presence of at least one of the following: impaired left ventricular function manifested by recent (≤100 days) congestive HF, or fractional shortening ≤25% by M-mode echocardiography; systolic blood pressure of >160 mmHg at study entry; prior ischaemic stroke, TIA or SE (i.e. prior TE); female sex or aged >75 years.

i Ischaemic stroke only.

(NASPEAF[39]) or previous evidence of obstructive disease (SPAF III[43]); SPORTIF III and V[67,69] required clinical and radiological evidence of arterial occlusion in the absence of another possible mechanism, and in the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism required angiographic demonstration of acute arterial occlusion. The AFASAK II[42] study did not define SE, but specified the sites of the event and required verification using angiography, surgery, scintigraphy or autopsy. From a clinical perspective, it was assumed that these different definitions of embolism were broadly similar and considered the same for the purposes of this review.

For the purpose of this review we are considering SE and TE as the same. It is assumed from the definitions of outcomes provided by the studies that TE refers to arterial TE not venous TE. From this point onwards the term *systemic embolism* (SE) will be used, but the original terms reported by the studies will be retained in the tables.

Two randomised comparisons[42,43] and the two pooled non-randomised comparisons[67,69] (*Table 13*) compared warfarin plus aspirin with warfarin alone in different regimes. The AFASAK II[42] study compared fixed-dose warfarin (1.25 mg daily) plus aspirin (300 mg daily) with adjusted-dose warfarin (INR 2.0–3.0) or fixed-dose warfarin (1.25 mg daily). The risk profile of the patients enrolled in the AFASAK II study[42] was not specified. The rate of stroke and systemic embolism (including fatal strokes) was the same among patients receiving the combination therapy and patients receiving adjusted-dose warfarin (INR 2.0–3.0) alone [12/171 (7.0%) vs 12/170 (7.1%), respectively, RR 0.99 (95% CI 0.46 to 2.15)] after a median follow-up period of 3.5 years.[42] A non-significant but numerically lower number of people experienced a stroke and systemic embolism among those receiving combination therapy than in those receiving fixed-dose warfarin alone [12/171 (7.0%) vs 14/167 (8.4%), respectively, RR 0.84 (95% CI 0.40 to 1.76)] during the median 3.5-year follow-up period.

The SPAF III[43] study compared adjusted-dose warfarin (INR 1.2–1.5) plus aspirin (325 mg daily) with adjusted-dose warfarin (INR 2.0–3.0) alone in high-risk patients with AF. The study[43] reported significantly more ischaemic strokes and systemic emboli among those receiving combination therapy than in those receiving adjusted-dose warfarin (INR 2.0–3.0) alone [44/521 (8.4%) vs 11/523 (2.1%), respectively; RR 4.02 (95% CI 2.10 to 7.69)] over a mean 1.1-year follow-up period.

The pooled analyses of the SPORTIF trials[67,69] compared combination adjusted-dose warfarin (INR 2.0–3.0) plus aspirin ≤ 100 mg with adjusted-dose warfarin (INR 2.0–3.0) alone, in a pooled analysis of SPORTIF III and V[69] and in a subgroup analysis of the pooled SPORTIF III and V[67] among those who had experienced an embolic event prior to enrolment. For the whole cohort, the rate of stroke and systemic embolism was very similar in patients receiving the combination therapy to those receiving adjusted-dose warfarin (INR 2.0–3.0) alone, 11 out of 481 (2.3%) versus 69 out of 3172 (2.2%), respectively, during the mean 16.5-month follow-up period.[69]

In the pooled analysis restricted to those patients with a previous embolic event prior to randomisation, the rate of stroke and systemic embolism was higher, but not significantly so, among those receiving combination therapy than in those receiving adjusted-dose warfarin (INR 2.0–3.0) alone [13/186 (6.9%) vs 23/567 (4.1%)] during the mean 16.6-month follow-up period.[67]

The rate of stroke and systemic embolism was much higher in the AFASAK II[42] and SPAF III[43] studies than in the pooled analysis of the SPORTIF trials[69] for those receiving combination therapy compared with warfarin alone. In the AFASAK II[42] and SPAF III[43] studies the rate of stroke and systemic embolism were 12 out of 171 (7.0%) and 44 out of 521 (8.4%), respectively, compared with 11 out of 481 (2.3%) in the pooled analysis of SPORTIF.[69]

The rate of stroke and systemic embolism was very similar among those receiving adjusted-dose warfarin alone in the SPAF III[43] study and the pooled analysis of the SPORTIF[69] trial [11/523 (2.1%) and 69/3172 (2.2%), respectively]. However, the rate of stroke and systemic embolism was much higher in the

AFASAK II[42] study for those receiving adjusted-dose warfarin (INR 2.0–3.0) alone or fixed-dose warfarin (1.25 mg) alone [12/170 (7.1%) and 14/167 (8.4%), respectively] compared with SPAF III[43] and the pooled analysis of SPORTIF.[69]

The rate of stroke and systemic embolism was very similar in AFASAK II[42] but higher in SPAF III[43] when compared with the pooled subgroup analysis of SPORTIF III and V restricted to patients with a previous embolic event,[67] for those receiving combination warfarin plus aspirin [12/171 (7.0%), 44/521 (8.4%) and 13/186 (6.9%), respectively]. The rate of stroke and systemic embolism was much higher among patients receiving either fixed or adjusted-dose warfarin alone in AFASAK II,[42] 14/167 (8.4%) and 12/170 (7.1%), respectively, during a median 3.5 year follow-up, and lower in SPAF III[43] for those receiving warfarin alone, 11/523 (2.1%) compared with those receiving warfarin alone in the pooled subgroup analysis of SPORTIF,[67] 23/567 (4.1%) during a mean/median 16.6 month follow-up. The variations in the rates may reflect the heterogeneity between included studies, as discussed above (see *Between-study differences*, above).

One randomised comparison (NASPEAF[39]) compared adjusted-dose acenocoumarol (INR 1.4–2.4) in combination with triflusal (600 mg) with adjusted-dose acenocoumarol (INR 2.0–3.0) alone in high-risk patients, and adjusted-dose acenocoumarol (INR 1.25–2.0) and triflusal (600 mg) in combination compared with adjusted-dose acenocoumarol (INR 2.0–3.0) alone in intermediate-risk patients.[39]

In the high-risk population, adjusted-dose acenocoumarol (INR 1.4–2.4) in combination with triflusal 600 mg was associated with a non-significant but numerically lower number of stroke and systemic embolism than adjusted-dose acenocoumarol (INR 2.0–3.0) alone [12/223 (5.4%) vs 20/247 (8.1%), respectively, RR 0.66 (95% CI 0.33 to 1.33)], after a median follow-up of 2.95 years.[39] Similarly, when analyses involved only stroke and fatal systemic embolism, adjusted-dose acenocoumarol (INR 1.4–2.4) in combination with triflusal 600 mg was associated with a non-significant but numerically lower number of stroke and systemic emboli than adjusted-dose acenocoumarol (INR 2.0–3.0) alone [4/223 (1.8%) vs 8/247 (3.2%), respectively, RR 0.55 (95% CI 0.17 to 1.81)].[39]

In the intermediate-risk population, adjusted-dose acenocoumarol (INR 1.25–2.0) in combination with triflusal 600 mg was also associated with a non-significant but numerically lower number of stroke and systemic embolism than adjusted-dose acenocoumarol (INR 2.0–3.0) alone [3/222 (1.4%) vs 7/232 (3.0%), respectively, RR 0.45 (95% CI 0.12 to 1.71)] after a median follow-up of 2.6 years.[39] Similarly, when analyses involved only stroke and fatal systemic embolism, adjusted-dose acenocoumarol (INR 1.25–2.0) in combination with triflusal 600 mg was associated with a non-significant but numerically lower number of stroke and systemic emboli than adjusted-dose acenocoumarol (INR 2.0–3.0) alone [0/222 (0%) vs 3/232 (1.3%), respectively, RR 0.15 (95% CI 0.01 to 2.87)].[39]

Three further articles provided post hoc analyses on the NASPEAF[44,45] and AFASAK II[47]studies; however, these papers simply reported duplicate data from the original studies.

In addition to the data on warfarin plus aspirin compared with warfarin alone, the pooled analyses of the SPORTIF III and V studies[67,69] also provide data on the risk of stroke and systemic embolism for patients receiving ximelagatran 36 mg given twice daily plus aspirin ≤ 100 mg compared with ximelagatran 36 mg alone.[67,69]

In the pooled analyses including all SPORTIF patients,[69] combination therapy yielded a slightly higher, but non-significant, rate of stroke and systemic embolism than in those receiving ximelagatran alone, 12/531 (2.3%) versus 58/3120 (1.9%), respectively, during the 16.5-month follow-up period.[69]

In just those patients with a previous embolic event, combination therapy yielded a rate of stroke and systemic embolism that was twice that of those receiving ximelagatran alone [11/157 (7.0%) vs 22/629 (3.5%), respectively], during a median 16.6-month follow-up, although this difference was not significant (RR 2.00, 95% CI 0.99 to 4.04).[67]

TABLE 13 Non-randomised comparisons for combined stroke and embolic events as outcome

Author, year	Stroke risk, follow-up	ACT + APT, *n*	No. of events/ total participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/ total participants in ACT arm (%)
Flaker *et al.*, 2006, pooled analysis of SPORTIF III and V[69]	High risk,[a] 16.5 months	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (≤100 mg), *n* = 481	Stroke[b]/SE: 11/481 (2.3)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 3172	Stroke[b]/SE: 69/3172 (2.2)
		Ximelagatran (36 mg) + aspirin (≤100 mg), *n* = 531	Stroke[b]/SE: 12/531 (2.3)	Ximelagatran (36 mg), *n* = 3120	Stroke[b]/SE: 58/3120 (1.9)
Akins *et al.*, 2006, pooled analysis of SPORTIF III and V cohort with previous embolic event[67]	High risk,[c] 16.6 months	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (≤100 mg), *n* = 156	Stroke[d]/SE: 13/186 (6.9)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 567	Stroke[d]/SE: 23/567 (4.1)
		Ximelagatran (36 mg) + aspirin (≤100 mg), *n* = 157	Stroke[d]/SE: 11/157 (7.0)	Ximelagatran (36 mg), *n* = 629	Stroke[d]/SE: 22/629 (3.5)

a At least one of the following: previous stroke/TIA/SE, hypertension, left ventricular dysfunction (ejection fraction <40% or symptomatic systolic or diastolic HF), age ≥75 years or age ≥65 years with known coronary disease/ diabetes mellitus.

b Also includes stroke due to ICH.

c Previous embolism.

d Ischaemic or haemorrhagic stroke.

Other pooled analyses of the SPORTIF III and V[68,71] trials are not presented in the table to avoid duplication of data.

The differences in stroke and systemic embolism outcomes reported in the included studies may reflect the methodological differences between these studies discussed in detail above (see *Between-study differences*).

Summary

There is no evidence, from two randomised[39,42] and two non-randomised[67,69] studies, of any benefit for combination therapy over anticoagulation alone in the reduction of the combined end point of stroke and SE. One randomised study suggests a significant increased risk of stroke and SE with the combination of ACT and APT compared with ACT alone.[43]

Outcome 4: systemic embolism

Eight studies, reported in 11 articles[39–45,47,52,54,61,73] yielded outcome data for SE alone. Of these, four studies[39–43] reported randomised comparisons (*Table 14*), supported by three subgroup analyses.[44,45,47] However, these subgroup analyses did not provide additional data for this outcome and, thus, are not considered further in this section (see *Appendix 7*).

Four studies[52,54,61,73] reported non-randomised comparisons; however, data from Blich *et al.*[61] and Toda *et al.*[52] are not reported further in this section (*Table 15*). The reasons for this can be found in *Appendix 7*.

TABLE 14 Randomised comparisons reporting the outcome of SE

Author, year	Stroke risk, follow-up	ACT + APT, *n*	No. of events/ total participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)	RR (95% CI)
[a]Pérez-Gómez *et al.*, 2004, RCT – NASPEAF[39]	High risk,[b] 2.95 years	Adjusted-dose acenocoumarol (INR 1.4–2.4) + triflusal (600 mg), *n* = 223	SE – non-fatal: 0/223 (0)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 247	SE non-fatal: 3/247 (1.2)	0.16 (0.01 to 3.05)
	Intermediate risk,[c] 2.6 year	Adjusted-dose acenocoumarol (INR 1.25–2.0) + triflusal (600 mg), *n* = 222	SE – non-fatal: 0/222 (0)	Acenocoumarol l adjusted dose (INR 2.0–3.0), *n* = 232	SE non-fatal: 1/232 (0.4)	0.35 (0.01 to 8.50)
Lechat *et al.*, 2001, RCT – FFAACS[41]	High risk,[d] 0.84 years	Adjusted-dose fluindione (INR 2.0–2.6) + aspirin (100 mg), *n* = 76	TE[e]: 2/76 (2.6)	Adjusted-dose fluindione (INR 2.0–2.6) + placebo, *n* = 81	TE:[e] 1/81 (1.2)	2.13 (0.20 to 23.03)
[f]Gullov *et al.*, 1998, RCT – AFASAK II[42]	Risk NR, 3.5 years	Fixed-dose warfarin (1.25 mg) + aspirin (300 mg), *n* = 171	TE[e]– all: 1/171 (0.6)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 170	TE:[e] all: 2/170 (1.2)	0.50 (0.05 to 5.43)
					TE:[e] fatal: 0/170 (0)	2.98 (0.12 to 72.70)
			TE[e] – fatal: 1/171 (0.6)	Fixed-dose warfarin (1.25 mg), *n* = 167	TE:[e] all: 1/167 (0.6)	0.98 (0.06 to 15.49)
					TE[e] – fatal: 1/167 (0.6)	0.98 (0.06 to 15.49)
SPAF investigators, 1996 RCT – SPAF III[43]	High risk,[g] 1.1 years	Adjusted-dose warfarin (INR 1.2–1.5) + aspirin (325 mg), *n* = 521	SE: 1/521 (0.2)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 523	SE: 0/523 (0)	3.01 (0.12 to 73.75)

NVAF, non-valvular atrial fibrillation.

a Supported by *n* = 2 subanalyses,[44,45] which provided duplicate data and are not presented in this table.

b Either NVAF with prior embolism or those with mitral stenosis with or without prior embolism.

c NVAF with no embolism at baseline.

d Presence of at least one: history of TE (TIA, non-disabling ischaemic stroke or peripheral embolism) or aged > 65 years and at least one of: history of hypertension (systolic arterial pressure of > 160 mmHg or diastolic arterial pressure > 90 mmHg); recent episode (< 3 months previously) of congestive HF or alteration in left ventricular function (echocardiographic left ventricular shortening fraction < 25% or LVEF < 40% within 3 months before study inclusion).

e For the purposes of this review, the terms SE and TE are classed as same because of broadly similar definitions in the included studies.

f Supported by *i* = 1 analysis 47, which provided duplicate data and are not presented in this table.

g Presence of at least one of the following: impaired left ventricular function manifested by recent (≤ 100 days) congestive HF, or fractional shortening ≤ 25% by M-mode echocardiography; systolic blood pressure > 160 mmHg at study entry; prior ischaemic stroke, TIA or SE (i.e. prior TE); female sex or aged > 75 years.

A precise definition of SE was not always given in the study reports and/or the definitions vary between studies. The NASPEAF,[39] FFAACS[41] and SPAF III[43] studies defined SE as an abrupt vascular insufficiency related to arterial occlusion, without previous clinical symptoms[39] or previous evidence of obstructive disease,[43] with one specifying the site of occlusion as affecting the mesenteric, renal, splenic or limb arteries.[41] The AFASAK II[42] study did not define a systemic embolic event, but specified the sites of the event and required verification using angiography, surgery, scintigraphy or autopsy. Of the two non-randomised comparisons, PETRO[73] defined a SE as an acute non-intracerebral or non-coronary vascular event, whereas Bover *et al.*[54] did not define SE.

Four studies,[41–43,54] three randomised comparisons[41,42,43] and one non-randomised comparison[54] compared a VKA plus aspirin with a VKA alone. The AFASAK II[42] and SPAF III[43] studies both compared warfarin plus aspirin with warfarin alone, although the warfarin and aspirin regimes differed between the studies. The FFAACS[41] study compared fluindione plus aspirin to fluindione alone, whereas one non-randomised comparison[54] compared acenocoumarol plus aspirin with acenocoumarol alone.

The AFASAK II[42] study compared fixed-dose warfarin (1.25 mg daily) plus aspirin (300 mg daily) with adjusted-dose warfarin (INR 2.0–3.0) or fixed-dose warfarin (1.25 mg daily). The risk profile of the patients enrolled in this study was not specified. The rates of SE were very small and there were no differences between groups during the median 3.5 years of follow-up; combination therapy compared with adjusted-dose warfarin (INR 2.0–3.0) alone [1/171 (0.6%) vs 2/170 (1.2%), respectively, RR 0.50 (95% CI 0.05 to

TABLE 15 Non-randomised comparisons reporting SE

Author, year, study name	Stroke risk, follow-up	ACT + APT, *n*	No. of events/total participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)
Bover *et al.*, 2009[54]	Risk NR, 4.92 years	Adjusted-dose acenocoumarol (INR 1.9–2.5) + triflusal (600 mg), *n* = 155	SE: 0/155 (0)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 265	SE: 7/265 (2.6)
		Acenocoumarol (INR 1.9–2.5) + triflusal (300 mg), *n* = 120	SE: 2/120 (1.7)		
		Acenocoumarol (INR 1.9–2.5) + aspirin (100 mg), *n* = 34	SE: 0/34 (0)		
[a]Ezekowitz *et al.*, 2007, PETRO[73]	High risk,[b] 22 weeks	Dabigatran (50 mg) + aspirin (81 mg), *n* = 21	TE:[c] 1/21 (4.8)	Dabigatran 50 mg (b.i.d.), *n* = 59	TE:[c] 1/59 (1.7)
		Dabigatran (50 mg) + aspirin (325 mg), *n* = 27	TE:[c] 0/27 (0)		
		Dabigatran (150 mg) + aspirin (81 mg), *n* = 36	TE:[c] 0/36 (0	Dabigatran 150 mg (b.i.d.), *n* = 100	TE:[c] 0/100 (0)
		Dabigatran (150 mg) + aspirin (325 mg), *n* = 33	TE:[c] 0/33 (0)		
		Dabigatran (300 mg) + aspirin (81 mg), *n* = 34	TE:[c] 0/34 (0)	Dabigatran 300 mg (b.i.d.), *n* = 105	TE:[c] 0/105 (0)
		Dabigatran (300 mg) + aspirin (325 mg), *n* = 30	TE:[c] 0/30 (0)		

b.i.d., dose administered twice daily; NR, not reported.

a Longitudinal study consisting of participants from the NASPEAF trial[39] in addition to new participants. Not all participants from the RCT were administered the therapies to which they were originally randomised.

b All patients with ST-segment elevation MI and undergoing PCI.

c For the purposes of this review, SE and TE are classed as same because of broadly similar definitions in the included studies.

5.43)] and compared with fixed-dose (1.25 mg) warfarin alone [1/171 (0.6%) vs 1/167 (0.6%), RR 0.98 (95% CI 0.06 to 15.49)]. The rates of fatal SE were also presented, but given the very low rates of all SE these do not add anything meaningful.[42]

The SPAF III[43] study compared adjusted-dose warfarin (INR 1.2–1.5) plus aspirin (325 mg daily) with adjusted-dose warfarin (INR 2.0–3.0) alone in high-risk patients with AF. One patient receiving combination therapy experienced a SE compared with no patients who received warfarin alone [(1/521 (0.2%) vs 0/523 (0%), respectively, RR 3.01 (95% CI 0.12 to 73.75)] during the mean 1.1-year follow-up period.[43]

The FFAACS[41] study compared adjusted-dose fluindione (INR 2.0–2.6) plus aspirin 100 mg with adjusted-dose fluindione (INR 2.0–2.6) alone. The rate of SE among patients receiving combination therapy was twice that of patients receiving fluindione alone [2/76 (2.6%) vs 1/81 (1.2%), respectively, RR 2.13 (95% CI 0.20 to 23.03)] during a mean 0.84-year follow-up, although this difference was not significant.

The non-randomised study by Bover *et al*.[54] provided additional data on the effect of a VKA plus aspirin compared with a VKA alone. This study compared adjusted-dose acenocoumarol (INR 1.9–2.5) in combination with aspirin (100 mg) with adjusted-dose acenocoumarol (INR 2.0–3.0). There were fewer systemic emboli during a mean 4.92-year follow-up in those receiving combination therapy than in those receiving acenocoumarol alone [0/34 (0%) vs 7/265 (2.6%), respectively; RR 0.51 (95% CI 0.03 to 8.68)], but the difference was not significant.[54]

In each study there were very few systemic embolic events. The rate was similar between the four studies[41–43,54] and between those receiving combination VKA plus aspirin and those receiving VKA therapy alone,[41–43,54] despite methodological and clinical differences between these studies (see *Between-study differences*).

The NASPEAF[39] randomised comparison compared adjusted-dose acenocoumarol (INR 1.4–2.4) in combination with triflusal 600 mg with adjusted-dose acenocoumarol (INR 2.0–3.0) alone in high-risk patients, and adjusted-dose acenocoumarol (INR 1.2–2.0) and triflusal 600 mg in combination compared with adjusted-dose acenocoumarol (INR 2.0–3.0) alone in intermediate-risk patients.

In both comparisons, no systemic embolic events occurred in patients receiving acenocoumarol in combination with triflusal, but a small number of patients in both the high- and intermediate-risk groups experienced a systemic embolic event with acenocoumarol alone [3/247 (1.2%) vs 1/232 (0.4%), respectively]. There were no statistically significant differences between combination therapy and anticoagulation treatment alone in either the high-risk (RR 0.16; 95% CI 0.01 to 3.05) or intermediate-risk (RR 0.35; 95% CI 0.01 to 8.50) populations after a median of 2.95 and 2.6 years of follow-up, respectively.[39]

One non-randomised study[54] compared adjusted-dose acenocoumarol (INR 1.9–2.5) in combination with triflusal (600 mg) with adjusted-dose acenocoumarol (INR 2.0–3.0) alone, and adjusted-dose acenocoumarol (INR 1.9–2.5) and triflusal (300 mg) in combination compared with adjusted-dose acenocoumarol (INR 2.0–3.0) alone. This study adds data to the randomised comparison in the NASPEAF[39] trial above.

Combination acenocoumarol (INR 1.9–2.5) with either triflusal 600 mg or triflusal 300 mg was associated with lower rates of SE, 0 out of 155 (0%) and 2 out of 120 (1.7%), respectively, than acenocoumarol alone, 7 out of 265 (2.6%), after a mean 4.92-year follow-up.[54]

One additional study, PETRO,[73] reported non-randomised comparisons for the outcome of SE.

The PETRO study[73] contained three comparisons: (1) dabigatran 50 mg (twice daily) plus aspirin (either 81 mg or 325 mg daily) compared with dabigatran 50 mg twice daily; (2) dabigatran 150 mg (twice daily) plus aspirin (either 81 mg or 325 mg daily) compared with dabigatran 150 mg twice daily; and (3)

dabigatran 300 mg (twice daily) plus aspirin (either 81 mg or 325 mg daily) compared with dabigatran 300 mg twice daily.

Systemic emboli occurred only in patients receiving combination dabigatran 50 mg (once/twice daily) plus aspirin 81 mg and dabigatran 50 mg twice daily alone. The proportion experiencing a SE was higher in patients receiving the combination therapy than in those receiving dabigatran alone [1/21 (4.8) vs 1/59 (1.7), respectively] after a 22-week follow-up period.[73]

The differences in SE outcomes reported in the included studies may reflect the methodological differences between these studies discussed in detail above (see *Between-study differences*).

Summary

Very few systemic emboli were reported. There is no evidence that combination ACT plus APT is associated with a significant reduction in systemic embolic events compared with ACT alone in six studies[39,41–43,54,73] (four randomised[39,41–43] and two non-randomised[54,73]).

Outcome 5: acute myocardial infarction

Five studies reported in nine articles[39,42–45,47,54,68,69] yielded outcome data for acute myocardial infarction (AMI) (or ACS). Of these, three studies in six articles[39,42–45,47] reported randomised comparisons. The key characteristics of these studies have been previously reported previously in *Table 4*.

The remaining three articles[54,68,69] reported non-randomised comparisons; one a primary study by Bover *et al*.[54] and two secondary analyses of the SPORTIF III and SPORTIF V studies by White *et al*.[68] and Flaker *et al*.[69] The characteristics of the studies reporting non-randomised comparisons have been reported previously in *Table 6*.

Only data from five of the included studies[39,42,43,54,69] have been reported in this section. Reasons for non-inclusion of data from other studies have been reported in *Appendix 7*.

The findings of the studies that report randomised comparisons are shown in *Table 16* and non-randomised comparisons in *Table 17*.

A precise definition of AMI and its subclassification was not always supplied in the study reports and/or the definitions varied between the studies. Among the included studies the AFASAK II trial[42] and the analysis of the SPORTIF III and SPORTIF V studies by Flaker *et al*.,[69] defined AMI by presence of any two assessment criteria, i.e. history of typical chest pain, serial creatine kinase MB isozyme changes typical of AMI, or electrocardiogram changes typical of AMI. The NASPEAF trial[39] reported data for non-fatal AMI. Definition of AMI was not specified in the SPAF III trial,[43] NASPEAF study[39] or in the study by Bover *et al*.[54]

The AFASAK II[42] and SPAF III[43] studies reported randomised comparisons for different regimes of combined warfarin plus additional aspirin compared with warfarin alone. The findings of these studies have been reported in *Table 16*.

The AFASAK II[42] study reported no AMI events among patients receiving the combination of fixed-dose warfarin (1.25 mg) plus aspirin (300 mg). The AMI event rate was lower but not significantly so among those receiving combination therapy than in those receiving either fixed-dose warfarin (1.25 mg) alone [0/171 (0%) vs 6/167 (3.6%), RR 0.08 (95% CI 0.00 to 1.32)] or adjusted-dose warfarin alone

TABLE 16 Randomised comparisons reporting AMI outcome

Author, year, study name	Risk, follow-up	ACT + APT, *n*	No. of events/total participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)	RR (95% CI)
[a]Pérez-Gómez *et al.*, 2004, RCT – NASPEAF[39]	High risk,[b] 2.95 years	Adjusted-dose acenocoumarol (INR 1.4–2.4) + triflusal (600 mg), *n* = 223	AMI:[d] 0/223 (0)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 247	AMI:[d] 0/247 (0)	Not estimable
	Intermediate risk,[c] 2.6 years	Adjusted-dose acenocoumarol (INR 1.25–2.0) + triflusal (600 mg), *n* = 222	AMI:[d] 0/222 (0)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 232	AMI:[d] 0/232 (0)	Not estimable
[e]Gullov *et al.*, 1998, RCT – AFASAK II[42]	Risk NR, 3.5 years	Fixed-dose warfarin (1.25 mg) + aspirin (300 mg), *n* = 171	AMI: 0/171 (0)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 170	AMI: 4/170 (2.4)	0.11 (0.01 to 2.04)
				Fixed-dose warfarin (1.25 mg), *n* = 167	AMI: 6/167 (3.6)	0.08 (0.00 to 1.32)
SPAF investigators, 1996, RCT – SPAF III[43]	High risk,[f] 1.1 years	Adjusted-dose warfarin (INR 1.2–1.5) + aspirin (325 mg), *n* = 521	AMI: 10/521 (1.9)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 523	AMI: 5/523 (1.0)	2.01 (0.69 to 5.83)

NR, not reported; NVAF, non-valvular atrial fibrillation.

a Supported by *n* = 2 subanalyses,[44,45] which provided duplicate data and are not presented in this table.

b Either NVAF with prior embolism or those with mitral stenosis with or without prior embolism.

c NVAF with no embolism at baseline.

d AMI specified non-fatal.

e Supported by *n* = 1 analysis 47, which provided duplicate data and are not presented in this table.

f Presence of at one of the following: impaired left ventricular function manifested by recent (≤100 days) congestive HF, or fractional shortening ≤25% by M-mode echocardiography; systolic blood pressure of >160 mmHg at study entry; prior ischaemic stroke; TIA or SE (i.e. prior TE); female sex or aged >75 years.

TABLE 17 Non-randomised comparisons reporting AMI outcome

Author, year	Stroke risk, follow-up	ACT + APT, *n*	No. of events/ total participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)
[a]Bover *et al.*, 2009 [54]	Risk NR, 4.92 years	Adjusted-dose acenocoumarol (INR 1.9–2.5) + triflusal (600 mg), *n* = 155	AMI: 0/155 (0)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 265	AMI: 5/265 (1.9)
		Adjusted-dose acenocoumarol (INR 1.9–2.5) + triflusal (300 mg), *n* = 120	AMI: 1/120 (0.8)		
		Adjusted-dose acenocoumarol (INR 1.9–2.5) + aspirin (100 mg), *n* = 34	AMI: 0/34 (0)		
Flaker *et al.*, 2006 [69]	High risk,[b] 16.5 months	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (≤ 100 mg), *n* = 481	AMI: 4/481 (0.8)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 3172	AMI: 46/3172 (1.5)
		Ximelagatran (36 mg) + aspirin (≤ 100 mg), *n* = 531	AMI: 10/531 (1.9)	Ximelagatran (36 mg), *n* = 3120	AMI: 40/3120 (1.3)

NR, not reported.

a Longitudinal study consisting of participants from the NASPEAF trial [39] in addition to new participants. Not all participants from the RCT were administered the therapies to which they were originally randomised.

b At least one of these risk factors: previous stroke/TIA/SE, hypertension, left ventricular dysfunction (ejection fraction < 40% or symptomatic systolic or diastolic HF), aged ≥ 75 years or aged ≥ 65 years with known coronary disease/ diabetes mellitus.

(INR 2.0–3.0) [0/171 (0%) vs 4/170 (2.4%), RR 0.11 (95% CI 0.01 to 2.04)] over a mean follow-up period of 3.5 years. The risk profile of the patients enrolled in this study[42] was not specified.

The SPAF III[43] study reported a non-significant but higher incidence of AMI events in the combined therapy group than in those receiving adjusted-dose warfarin (INR 2.0–3.0) alone [10/521 (1.9%) vs 5/523 (1.0%), respectively], RR 2.01 (95% CI 0.69 to 5.83), in high-risk patients over a mean follow-up period of 1.1 years.[43]

The AMI rate was different in these two RCTs. Rates of AMI were higher in the combined therapy arm of the SPAF III study than those receiving combination therapy in the AFASAK II[42] study [1.9% (10/521) vs 0% (0/171), respectively]. However, the AMI rates were lower in those receiving adjusted-dose warfarin (INR 2.0–3.0) alone in the SPAF III study[43] [5/523 (1.0%)] than in those receiving either adjusted-dose warfarin alone or fixed-dose warfarin alone [(4/170 (2.4%) and 6/167 (3.6%), respectively] in the AFASAK II study.[42]

Flaker *et al.*,[69] in their post hoc analysis of non-randomised comparisons from the SPORTIF III and V studies, reported fewer AMI events in the combined therapy than in those on adjusted-dose warfarin (INR 2.0–3.0) alone [4/481 (0.8%) vs 46/3172 (1.5%), respectively] over a mean follow-up period of 16.5 months. However, aspirin was indicated in patients with previous CAD in the SPORTIF studies.[64,65]

Bover *et al.*[54] compared adjusted-dose acenocoumarol (INR 1.9–2.5) plus aspirin (100 mg) with adjusted-dose acenocoumarol alone (INR 2.0–3.0) over a mean follow-up period of 4.92 years. This study also

compared combination acenocoumarol and two different regimes of triflusal, which will be discussed in a subsequent section. The findings of this study for the outcome of AMI are reported in *Table 17*.

No AMIs occurred in the 34 patients receiving combination acenocoumarol and aspirin compared with 5 out of 265 (1.9%) AMIs in those receiving acenocoumarol alone.[54] The rate of AMIs was lower in all three combination therapy arms than in the arm with adjusted-dose acenocoumarol alone. No AMIs occurred in those receiving acenocoumarol plus triflusal 600 mg or acenocoumarol plus aspirin 100 mg, and one patient receiving acenocoumarol plus triflusal 300 mg experienced an AMI [1/120 (0.8%)] compared with 5 out of 265 (1.9%) patients receiving adjusted-dose warfarin alone.

Flaker *et al*.[69] also reported non-randomised comparisons for ximelagatran (36 mg) plus aspirin (100 mg) with ximelagatran (36 mg) alone, over a mean follow-up period of 16.5 months. A slightly higher rate of AMIs was observed in patients on combined therapy than in those on ximelagatran alone [10/531 (1.9%) vs 40/3120 (1.3%), respectively]. However, it is to be noted that aspirin use was indicated in patients with previous CAD in the original SPORTIF studies.[65,68]

No studies were identified that reported randomised comparisons for AMI outcome comparing ximelagatran in combination with aspirin with ximelagatran alone.

The NASPEAF study[39] compared adjusted-dose acenocoumarol (INR 1.4–2.4) plus triflusal (600 mg) with adjusted-dose acenocoumarol alone (INR 2.0–3.0) in high-risk patients during a median follow-up of 2.95 years, and combination adjusted-dose acenocoumarol (INR 1.2–2.0) plus triflusal (600 mg) with adjusted-dose acenocoumarol alone (INR 2.0–3.0) in intermediate-risk patients during a median follow-up of 2.6 years. This study specified outcomes for non-fatal AMIs. No non-fatal AMIs occurred in the NASPEAF study.[39]

Bover *et al*.[54] reported non-randomised AMI outcome data comparing adjusted-dose acenocoumarol (INR 1.9–2.5) plus triflusal in two different regimes (600 mg or 300 mg) or aspirin (100 mg) with adjusted-dose acenocoumarol (INR 2.0–3.0) alone, over a mean follow-up period of 4.92 years.

The rate of AMI was lower in all three combination therapy arms than for adjusted-dose acenocoumarol alone. No AMIs occurred in those receiving acenocoumarol plus triflusal 600 mg or acenocoumarol plus aspirin 100 mg, and one patient receiving acenocoumarol plus triflusal 300 mg experienced an AMI [1/120 (0.8%)] compared with 5 out of 265 (1.9%) patients receiving adjusted-dose acenocoumarol alone.

The combination of adjusted-dose acenocoumarol (target INR 1.9–2.5) with either triflusal 600 mg or triflusal 300 mg or aspirin (100 mg) demonstrated fewer events of AMI [1/155 (0%), 1/120 (0.8%) and 0/34 (0%), respectively] than acenocoumarol given alone in adjusted dose alone with target INR of 2.0–3.0 [5/265 (1.9%)].

The differences in AMI outcomes reported in the included studies may reflect the methodological differences between these studies discussed in detail above (see *Between-study differences*). In addition, only two studies,[42,69] one randomised[42] and one non-randomised[69] provided a specific definition for AMI, whereas three others[39,43,54] (two randomised[39,43] and one non-randomised[54]) did not. Both the AFASAK II[42] and SPORTIF III and V[69] studies used the same standard definition of AMI. Four studies[42,43,54,69] (two randomised[42,43] and two non-randomised[54,69]) reported all AMIs, whereas one randomised study[39] reported only non-fatal AMI events. Of note here for the non-randomised comparisons[54,69] is the potential confounding of the addition of APT to ACT at physicians' discretion, which may have resulted in patients at risk of an AMI being given APT, which may account for variation in the reported event rates.

Summary

Very few AMIs were reported. Although the rate of AMI was numerically lower with combined ACT plus APT compared with ACT alone in four[42,43,54,69] (two randomised[42,43] and two non-randomised[54,69]) of five[43] studies reporting this outcome, there was no evidence of a significant benefit of combination therapy in the reduction of AMIs. However, in the non-randomised comparisons the addition of APT is confounded by indication.[54,69]

Outcome 6: in-stent thrombosis

No studies were identified that reported in-stent thrombosis outcome data comparing ACT plus APT with anticoagulant alone in an AF population.

Outcome 7: vascular death

Four studies, reported in seven articles[39,41–45,47] yielded outcome data for vascular death. Of these, all four studies reported randomised comparisons[39,41–43] (*Table 18*) supported by three subgroup analyses.[44,45,47] No non-randomised comparisons reported vascular death as an outcome.

Vascular death was defined as sudden or any other death occurring within 30 days after a vascular event or progressive HF in the NASPEAF study.[39] The FFAACS study[41] reported vascular death as one due to any of the following reasons: ischaemic or haemorrhagic stroke (Rankin score between 4 and 5 followed by death), an AMI, sudden, fatal SE, fatal haemorrhage, arterial aneurysm rupture, gangrene secondary to severe ischaemia and/or pulmonary embolism.[41] Vascular death was not defined separately in the AFASAK II study[42] or the SPAF III study.[43] The definitions were considered broadly similar for the purposes of this review.

Three randomised comparisons[41–43] compared a VKA plus aspirin with a VKA alone. The AFASAK II[42] and SPAF III[43] studies both compared warfarin plus aspirin with warfarin alone, although the warfarin and aspirin regimes differed between the studies. The FFAACS[41] study compared fluindione plus aspirin with fluindione alone.

The AFASAK II[42] study compared fixed-dose warfarin (1.25 mg daily) plus aspirin (300 mg daily) with adjusted-dose warfarin (INR 2.0–3.0) or fixed-dose warfarin (1.25 mg daily). The risk profile of the patients enrolled in this study was not specified. The rates of vascular death were low and there were no significant differences in the rate of vascular death between the treatment groups during the median 3.5 years of follow-up: combination therapy compared with adjusted-dose warfarin (INR 2.0–3.0) alone [3/171 (1.8%) vs 5/170 (2.9%), respectively, RR 0.60 (95% CI 0.14 to 2.46)] and compared with fixed-dose (1.25 mg) warfarin alone [3/171 (1.8%) vs 2/167 (1.2%), respectively, RR 1.46 (95% CI 0.25 to 8.66)].[42]

The SPAF III[43] study compared adjusted-dose warfarin (INR 1.2–1.5) plus aspirin (325 mg daily) with adjusted-dose warfarin (INR 2.0–3.0) alone in high-risk patients with AF. The rate of vascular death was the same in both the combination therapy and warfarin-alone arms [27/521 (5.2%) vs 27/523 (5.2%), respectively, RR 1.00 (95% CI 0.6 to 1.69)] during the mean 1.1-year follow-up period.[43]

The FFAACS[41] study compared adjusted-dose fluindione (INR 2.0–2.6) plus aspirin 100 mg with adjusted-dose fluindione (INR 2.0–2.6) alone. The number of vascular deaths in both groups was small and the difference was not significant [3/76 (3.9%) vs 2/81 (2.5%), respectively, RR 1.60 (95% CI 0.27 to 9.31)] during a mean 0.84-year follow-up.

The rate of vascular death differed between the studies. Among those patients receiving combination therapy, the rate of vascular death was highest in the SPAF III[43] study: 27 out of 521 patients (5.2%) compared with 3 out of 171 patients (1.8%) in the AFASAK II[42] study and 3 out of 76 patients (3.9%) in the FFAACS study.[41] Among those receiving anticoagulation alone, again the rate of vascular death was

TABLE 18 Randomised comparison reporting vascular death as an outcome

Author, year	Stroke risk, follow-up	ACT + APT, *n*	No. of events/total participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)	RR (95% CI)
[a]Pérez-Gómez *et al.*, 2004, RCT – NASPEAF[39]	High risk,[b] 2.95 years	Adjusted-dose acenocoumarol (INR 1.4–2.4) + triflusal (600 mg), *n* = 223	Vascular all: 6/223 (2.7)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 247	Vascular all: 17/247 (6.9)	0.39 (0.16 to 0.97)
			• Vascular (bleed): 1/223 (0.4)		• Vascular (bleed): 0/247 (0)	3.32 (0.14 to 81.12)
			• Vascular (SE): 0/223 (0)		• Vascular (SE): 2/247 (0.8)	0.22 (0.01 to 4.59)
			• Vascular (stroke): 4/223 (1.8)		• Vascular (stroke): 6/247 (2.4)	0.74 (0.21 to 2.58)
			• Vascular (AMI): 0/223 (0)		• Vascular (AMI): 1/247 (0.4)	0.37 (0.02 to 9.01)
			• Vascular (HF): 0/223 (0)		• Vascular (HF): 2/247 (0.8)	0.22 (0.01 to 4.59)
			• Vascular (HF-avascular): 0/223 (0)		• Vascular (HF- avascular): 2/247 (0.8)	0.22 (0.01 to 4.59)
			• Vascular (sudden): 1/223 (0.4)		• Vascular (sudden): 4/247 (1.6)	0.28 (0.03 to 2.46)
	Intermediate risk,[c] 2.6 years	Adjusted-dose acenocoumarol (INR 1.25–2.0) + triflusal (600 mg), *n* = 222	Vascular all: 2/222 (0.9)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 232	Vascular all: 11/232 (4.7)	0.19 (0.04 to 0.85)
			• Vascular (bleed): 1/222 (0.5)		• Vascular (bleed): 0/232 (0)	3.13 (0.13 to 76.54)
			• Vascular (SE): 0/222 (0)		• Vascular (SE): 0/232 (0)	Not estimable
			• Vascular (stroke): 0/222 (0)		• Vascular (stroke): 3/232 (1.3)	0.15 (0.01 to 2.87)
			• Vascular (AMI): 0/222 (0)		• Vascular (AMI): 0/232 (0)	Not estimable
			• Vascular (HF): 0/222 (0)		• Vascular (HF): 3/232 (1.3)	0.15 (0.01 to 2.87)
			• Vascular (HF- avascular): 0/222 (0)		• Vascular (HF- avascular): 1/232 (0.4)	0.35 (0.01 to 8.50)
			• Vascular (sudden): 1/222 (0.5)		• Vascular (sudden): 4/232 (1.7)	0.26 (0.03 to 2.32)

continued

TABLE 18 Randomised comparison reporting vascular death as an outcome

Author, year	Stroke risk, follow-up	ACT + APT, *n*	No. of events/total participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)	RR (95% CI)
Lechat *et al.*, 2001 RCT – FFAACS[41]	High risk,[d] 0.84 years	Adjusted-dose fluindione (INR 2.0–2.6) + aspirin (100 mg), *n* = 76	Vascular: 3/76 (3.9)	Adjusted-dose fluindione (INR 2.0–2.6) + placebo, *n* = 81	Vascular: 2/81 (2.5)	1.60 (0.27 to 9.31)
[e]Gullov *et al.*, 1998 RCT – AFASAK II[42]	Risk NR, 3.5 years	Fixed-dose warfarin (1.25 mg) + aspirin (300 mg), *n* = 171	Vascular: 3/171 (1.8)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 170	Vascular: 5/170 (2.9)	0.60 (0.14 to 2.46)
				Fixed-dose warfarin (1.25 mg), *n* = 167	Vascular: 2/167 (1.2)	1.46 (0.25 to 8.66)
SPAF investigators, 1996 RCT – SPAF III[43]	High risk,[f] 1.1 years	Adjusted-dose warfarin (INR 1.2–1.5) + aspirin (325 mg), *n* = 521	Vascular: 27/521 (5.2)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 523	Vascular: 27/523 (5.2)	1.00 (0.60 to 1.69)

NR, not reported; NVAF, non-valvular atrial fibrillation.

a Supported by *n* = 2 subanalyses,[44,45] which provided duplicate data and are not presented in this table.

b Either NVAF with prior embolism or those with mitral stenosis with and without prior embolism.

c NVAF with no embolism at baseline.

d Presence of at least one of history of TE (TIA, non-disabling ischaemic stroke or peripheral embolism) or aged >65 years, and at least one of history of hypertension (systolic arterial pressure of >160 mmHg or diastolic arterial pressure of >90 mmHg); recent episode (<3 months previously) of congestive HF or alteration in left ventricular function (echocardiographic left ventricular shortening fraction of <25% or LVEF<40% within 3 months before study inclusion).

e Supported by *n* = 1 analysis,[47] which provided duplicate data and are not presented in this table.

f Presence of at least one of the following: impaired LV function manifested by recent (≤100 days) congestive heart disease, or fractional shortening ≤25% by M-mode echocardiography; systolic blood pressure of >160 mmHg at study entry; prior ischaemic stroke, TIA or SE (i.e. prior TE); female sex or aged >75 years.

highest in the SPAF III study,[43] 27 out of 523 (5.2%) patients, with rates of 1.2% (2/167) and 2.9% (5/170) among those fixed- and adjusted-dose warfarin in the AFASAK II study, respectively, and 2.5% (2/81) in those patients receiving fluindione in the FFAACSs.[41] The NASPEAF[39] randomised comparison compared adjusted-dose acenocoumarol (INR 1.4–2.4) in combination with triflusal 600 mg with adjusted-dose acenocoumarol (INR 2.0–3.0) alone in high-risk patients and adjusted-dose acenocoumarol (INR 1.2–2.0) and triflusal 600 mg in combination compared with adjusted-dose acenocoumarol (INR 2.0–3.0) alone in intermediate-risk patients.

Fewer vascular deaths occurred in patients receiving combination therapy than in those receiving acenocoumarol alone in both the high-risk [6/223 (2.7%) vs 17/247 (6.9%), respectively] and intermediate-risk [2/222 (0.9%) vs 11/232 (4.7%), respectively] groups, but these differences were not significant: RR 0.39 (95% CI 0.16 to 0.97) and RR 0.19 (95% CI 0.04 to 0.85), respectively.

No studies reported non-randomised comparisons of ACT plus APT compared with ACT alone for the outcome of vascular death.

The differences in vascular mortality reported in the included studies may reflect the methodological differences between these studies discussed in detail above (see *Between-study differences*). Of the four randomised studies,[39,41–43] only two provided a specific definition of vascular death,[39,41] which may reflect the variation in vascular mortality reported between the included studies.

Summary

Very few vascular deaths occurred and the available evidence from four randomised studies suggests that combination ACT and APT does not significantly reduce the risk of vascular death compared with ACT alone.[39,41–43]

Secondary outcomes

Outcome 8: all-cause mortality

Ten articles[39,41–43,47,50,54,58,68,69] yielded outcome data for all-cause mortality. Of these, four studies in five articles[39,41–43,47] reported randomised comparisons. The remaining five articles[50,54,58,68,69] reported non-randomised comparisons, of which three were primary studies,[54,54,58] and two were secondary analyses of the SPORTIF III and SPORTIF V studies by White *et al*.[68] and Flaker *et al*.[69]

Of the studies that reported non-randomised comparisons, those by Lopes *et al*.,[50] Stenestrand *et al*.[58] and White *et al*.[68] are not mentioned further in this section because two of these[50,68] did not furnish details of number of patients (denominator) in either therapy group and one did not report the number of events.[58] The reasons for non-inclusion of their data have been reported in *Appendix 7*. The characteristics of these studies have been reported previously (see *Table 6*).

All-cause mortality was frequently classified as death from non-vascular, indeterminant, unknown or sudden causes. A precise definition of these groupings or subclassifications of mortality was not always supplied in the study reports and/or the definitions may vary between studies for the same subclassification.

The findings of the included studies for each of these composites and/or subclassifications of all-cause mortality are detailed in *Tables 19* and *20*.

All-cause mortality

Two randomised comparisons (AFASAK II[42] and SPAF III[43]) and one non-randomised comparison[69] compared the combination of warfarin plus aspirin with warfarin alone.

The AFASAK II[42] randomised comparison compared combined fixed-dose warfarin (1.25 mg) plus aspirin (300 mg daily) with either adjusted-dose warfarin (target INR 2.0–3.0) alone or with fixed-dose warfarin (1.25 mg daily) alone. The risk profile of the patients enrolled in this study was not specified. The rate of all-cause mortality was lower among those patients receiving combined therapy than in those receiving fixed-dose warfarin [9/171 (5.3%) vs 17/170 (10%), respectively, RR 0.53 (95% CI 0.24 to 1.15)] and higher than those patients receiving adjusted-dose warfarin [9/171 (5.3%) vs 6/167 (3.6%), respectively, RR 1.46 (95% CI 0.53 to 4.03)] over a mean follow-up period of 3.5 years, although these differences were not significant.[42] The SPAF III study[43] compared adjusted-dose warfarin (INR 1.2–1.5) plus aspirin (325 mg) with adjusted-dose warfarin (target INR 2.0–3.0) alone in high-risk patients with AF. The study[43] demonstrated similar rates of all-cause mortality for patients treated with adjusted-dose warfarin (INR1.2–1.5) in combination with aspirin (325 mg) compared with those treated with adjusted-dose warfarin (INR 2.0–3.0) alone [42/521 (8.1%) vs 35/523 (6.7%), respectively, RR 1.20 (95% CI 0.78 to 1.86)] over a mean follow-up period of 1.1 years.

There were small differences in the rate of all-cause mortality in these two RCTs.[42,43] In the combination therapy arm of the SPAF III study[43] the mortality rate was slightly higher at 8.1% (42/521) than 5.3% (9/171) in the combined therapy arm in the AFASAK II study.[42] Among those patients receiving adjusted-dose warfarin alone, the rate of all-cause mortality was also higher in the SPAF III[43] study [35/523 (6.7%)] than in the AFASAK II[42] study [6/167 (3.6%)], but lower than those receiving fixed-dose warfarin alone in the AFASAK II study[42] [35/523 (6.7%) vs 17/170 (10%), respectively].

The pooled analysis of the SPORTIF studies by Flaker *et al*.[69] compared adjusted-dose warfarin (INR 2.0–3.0) plus aspirin (100 mg) with adjusted-dose warfarin (INR 2.0–3.0) alone, over a mean follow-up period of 16.5 months. The rate of all-cause mortality was the same in patients receiving combined therapy or warfarin alone [17/481 (3.5%) vs 112/3172 (3.5%), respectively].

The mortality rate was much higher in the combined therapy arm of the AFASAK II[42] and SPAF III[43] studies than in the combined therapy arm in the SPORTIF III and V[69] studies [9/171 (5.3%), 42/521 (8.1%) and 17/481 (3.5%), respectively]. The mortality rate was also much higher in patients receiving adjusted-dose warfarin alone in the SPAF III[43] study [35/523(6.7%)] and fixed-dose warfarin alone in the AFASAK II[42] study [17/170 (10%)], but similar among those patients receiving adjusted-dose warfarin alone in the AFASAK II[42] and SPORTIF III and V studies [6/167 (3.6%) and 112/3172 (3.5%), respectively].

One study (NASPEAF[39]) reported randomised comparisons on all-cause mortality comparing adjusted-dose acenocoumarol (INR 1.4–2.4) plus triflusal (600 mg) with acenocoumarol alone (INR 2.0–3.0) in high-risk patients, and the combination of adjusted-dose acenocoumarol (INR 1.2–2.0) plus triflusal (600 mg) with acenocoumarol alone (INR 2.0–3.0) in intermediate-risk patients. The findings of this study are presented in *Table 19*.

The study demonstrated lower rates of all-cause mortality with combined therapy than acenocoumarol alone in the high-risk group [12/223 (5.4%) vs 23/247 (9.3%), respectively; RR 0.58 (95% CI 0.29 to 1.13)] over a median 2.95 year follow-up period, as well as in the intermediate-risk group [6/222 (2.7%) vs 20/232(8.6%), respectively; RR 0.31 (95% CI 0.13 to 0.77), over a median follow-up of 2.6 years, although these differences were not significant.

There was no non-randomised evidence available for all-cause mortality for this comparison.

The FFAACS[41] study demonstrated very similar rates of all-cause mortality for patients treated with adjusted-dose fluindione (INR 2.0–2.6) in combination with aspirin (100 mg) to those with adjusted-dose

TABLE 19 Randomised comparisons reporting the outcome of all-cause mortality

Author, year	Stroke risk, follow-up	ACT + APT, *n*	No. of events/total participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)	RR (95% CI)
Pérez-Gómez *et al.*, 2004, RCT – NASPEAF[39]	High risk,[a] 2.95 years	Adjusted-dose acenocoumarol (INR 1.4–2.4) + triflusal (600 mg), *n* = 223	Total:[b] 12/223 (5.4)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 247	Total:[b] 23/247 (9.3)	0.58 (0.29 to 1.13)
			Non-vascular: 6/223 (2.7)		Non-vascular: 6/247 (2.4)	1.11 (0.36 to 3.38)
	Intermediate risk,[c] 2.6 years	Adjusted-dose acenocoumarol (INR 1.25–2.0) + triflusal (600 mg), *n* = 222	Total:[b] 6/222 (2.7)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 232	Total:[b] 20/232 (8.6)	0.31 (0.13 to 0.77)
			Non-vascular: 4/222 (1.8)		Non-vascular: 9/232 (3.9)	0.46 (0.15 to 1.49)
Lechat *et al.*, 2001 RCT – FFAACS[41]	High risk,[d] 0.84 years	Adjusted-dose fluindione (INR 2.0–2.6) + aspirin (100 mg), *n* = 76	All cause: 3/76 (3.9)	Adjusted-dose fluindione (INR 2.0–2.6) + placebo, *n* = 81	All cause: 3/81 (3.7)	1.07 (0.22 to 5.12)
[e]Gullov *et al.*, 1998 RCT – AFASAK II[42]	Risk NR, 3.5 years	Fixed-dose warfarin (1.25 mg) + aspirin (300 mg), *n* = 171	Total:[f] 9/171 (5.3)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 170	Total:[f] 6/167 (3.6)	1.46 (0.53 to 4.03)
			Non-vascular: 1/171 (0.6)		Non-vascular: 0/167 (0)	2.93 (0.12 to 71.42)
			Unknown cause: 2/171 (1.2)		Unknown cause: 2/167 (1.2)	0.98 (0.14 to 6.85)
				Fixed-dose warfarin (1.25 mg), *n* = 167	Total:[f] 17/170 (10.0)	0.53 (0.24 to 1.15)
					Non-vascular: 2/170 (1.2)	0.50 (0.05 to 5.43)
					Unknown cause: 3/170 (1.8)	0.66 (0.11 to 3.92)
SPAF investigators, 1996 RCT – SPAF[43]	High risk,[f] 1.1 years	Adjusted-dose warfarin (INR 1.2–1.5) + aspirin (325 mg), *n* = 521	Total:[f] 42/521 (8.1)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 523	Total:[f] 35/523 (6.7)	1.20 (0.78 to 1.86)
			Non-vascular: 12/521 (2.3)		Non-vascular: 8/523 (1.5)	1.51 (0.62 to 3.65)
			Indeterminant: 3/521 (0.6)		Indeterminant: 0/523 (0)	7.00 (0.36 to 135.18)

NR, not reported; NVAF, non-valvular atrial fibrillation.

a Either NVAF with prior embolism or those with mitral stenosis with and without prior embolism.

b Includes vascular, non-vascular.

c NVAF with no embolism at baseline.

d Presence of at least one of history of TE (TIA, non-disabling ischaemic stroke or peripheral embolism) or aged >65 years, and at least one of history of hypertension (systolic arterial pressure >160 mmHg or diastolic arterial pressure >90 mmHg); recent episode (<3 months previously) of congestive HF or alteration in left ventricular function (echocardiographic left ventricular shortening fraction <25% or LVEF of <40% within 3 months before study inclusion).

e Supported by *n* = 1 analysis,[47] which provided duplicate data and are not presented in this table.

f Includes vascular, non-vascular, indeterminant or unknown.

g Presence of at least one of impaired LV function manifested by recent (≤100 days); congestive heart disease, or fractional shortening ≤25% by M-mode echocardiography; systolic blood pressure of >160 mmHg at study entry; prior ischaemic stroke, transient ischaemic attack or systemic embolism (i.e., prior TE); female sex or aged >75 years.

TABLE 20 Non-randomised comparisons reporting the outcome of all-cause mortality

Author, year	Stroke risk, follow-up	ACT + APT, *n*	No. of events/total participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/ total participants in ACT arm (%)
Bover *et al.*, 2009[54]	Risk NR, 4.92 years	Adjusted-dose acenocoumarol (INR 1.9–2.5) + triflusal (600 mg), *n* = 155	Non-cardiac: 6/155 (3.9) Sudden: 4/155 (2.6)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 265	–
		Adjusted-dose acenocoumarol (INR 1.9–2.5) + triflusal (300 mg), *n* = 120	Non-cardiac: 3/120 (2.5) Sudden: 0/120 (0)		Non-cardiac: 3/265 (1.1) Sudden: 3/265 (1.1)
		Adjusted-dose acenocoumarol (INR 1.9–2.5) + aspirin (100 mg), *n* = 34	Non-cardiac: 1/34 (2.9) Sudden: 1/34 (2.9)		
Flaker *et al.*, 2006[69]	High risk,[a] 16.5 months	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (≤ 100 mg), *n* = 481	All: 17/481 (3.5)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 3172	All: 112/3172 (3.5)
		Ximelagatran (36 mg) + aspirin (≤ 100 mg), *n* = 531	All: 3/531 (0.6)	Ximelagatran (36 mg), *n* = 3120	All: 95/3120 (3.0)

NR, not reported.

a At least one of the risk factors: previous stroke/TIA/SE, hypertension, left ventricular dysfunction (ejection fraction < 40% or symptomatic systolic or diastolic HF), aged ≥ 75 years or aged ≥ 65 years with known coronary disease/ diabetes mellitus.

fluindione (INR 2.0–2.6) plus placebo [3/76 (3.9%) vs 3/81 (3.7%), respectively; RR 1.07 (95% CI 0.22 to 5.12], over a mean follow-up period of 0.84 years.

There was no non-randomised evidence available for all-cause mortality for this comparison.

The pooled analysis of SPORTIF trials by Flaker *et al.*[69] reported non-randomised comparisons for all-cause mortality comparing ximelagatran (36 mg) plus aspirin (100 mg) with ximelagatran (36 mg) alone, over a mean follow-up period of 16.5 months. Fewer deaths were observed in patients on combined therapy than in those on ximelagatran alone [3/531 (0.6%) vs 95/3120 (3.0%), respectively]. However, it is to be noted that aspirin use was based on clinical need and thus the comparison may be confounded by indication.[65,68]

There was no randomised evidence available for all-cause mortality for this comparison.

Summary

Five studies demonstrated that combination therapy with ACT and APT did not confer a reduction in all-cause mortality over ACT alone (three randomised[39,41,42] and two non-randomised[54,69]).

Mortality due to non-vascular causes

The AFASAK II[42] and SPAF III[43] studies reported randomised comparisons for mortality due to non-vascular causes comparing combinations of different regimes of warfarin plus aspirin to warfarin alone. There were no non-randomised comparisons identified for this outcome.

The AFASAK II[42] RCT demonstrated similar rates of mortality due to non-vascular causes in patients receiving the combination of fixed-dose warfarin (1.25 mg) and aspirin (300 mg) compared with those receiving fixed-dose warfarin (1.25 mg) alone [1/171 (0.6%) vs 2/170 (1.2%), respectively); RR 0.50 (95% CI 0.05 to 5.43)] over a mean follow-up period of 3.5 years. No non-vascular deaths occurred in patients receiving adjusted-dose warfarin (INR 2.0–3.0) alone [1/171 (0.6%) vs 0/167 (0%), respectively); RR 2.93 (95% CI 0.12 to 71.42)]. The stroke risk of this population was not specified.[42]

The SPAF III[43] study demonstrated similar rates of mortality due to non-vascular causes in high-risk patients treated with adjusted-dose warfarin (INR 1.2–1.5) plus aspirin (325 mg) compared with those treated with adjusted-dose warfarin (INR 2.0–3.0) alone [12/521 (2.3%) vs 8/523(1.5%), respectively); RR 1.51 (95% CI 0.62 to 3.65)] over a mean follow-up period of 1.1 years.[43]

There were very few non-vascular deaths in these two RCTs.[42,43] In the combination therapy arms, the event rate was higher in the SPAF III[43] study at 2.3% (12/521) compared with 0.6% (1/171) in the AFASAK II study.[42] Rates of non-vascular mortality were similar in those receiving adjusted-dose warfarin alone in the SPAF III[43] study [8/523 (1.5%)] and fixed-dose warfarin in the AFASAK II study [2/170 (1.2%)]. No non-vascular deaths occurred in the AFASAK II[42] study among patients receiving adjusted-dose warfarin. The differences might reflect the methodological heterogeneity between studies as explained previously (see *Between-study differences*).

The NASPEAF[39] study reported randomised comparisons on non-vascular cause mortality comparing adjusted-dose acenocoumarol (INR 1.4–2.4) plus triflusal (600 mg) with acenocoumarol alone (INR 2.0–3.0) in high-risk patients, and the combination of adjusted-dose acenocoumarol (INR 1.2–2.0) plus triflusal (600 mg) with acenocoumarol alone (INR 2.0–3.0) in intermediate-risk patients. The findings of this study are presented in *Table 19*.

The study demonstrated similar rates of non-vascular death when combined therapy was compared with acenocoumarol alone in the high-risk group [6/223 (2.7%) vs 6/247(2.4%), respectively; RR 1.11 (95% CI 0.36 to 3.38)] and lower but non-significant non-vascular mortality rates in the intermediate-risk group on combined therapy compared with those on acenocoumarol alone [4/222 (1.8%) vs 9/232 (0.48%), respectively; RR 0.46 (95% CI 0.15 to 10.49].

There were no non-randomised comparisons identified for this outcome.

Summary

Combination therapy with ACT and APT did not confer a reduction in non-vascular mortality over ACT alone in two randomised studies.[39,42]

Mortality due to indeterminant or unknown cause

The AFASAK II[42] and SPAF III[43] studies reported randomised comparisons for mortality due to unknown causes comparing combinations of different regimes of warfarin plus aspirin with warfarin alone. There were no non-randomised comparisons identified for this outcome.

The AFASAK II study[42] demonstrated similar rates of mortality from unknown causes across all arms (see *Table 19*). The event rate was 1.2% in patients receiving combination therapy (2/171) and those receiving adjusted-dose warfarin alone [2/167); RR 0.98 (95% CI 0.14 to 6.85)] and similar in those receiving fixed-dose warfarin alone [3/170 (1.8%); RR 0.66 (95% CI 0.11 to 3.92)] over a mean follow-up period of 3.5 years. The stroke risk of this population was not specified.[42]

The SPAF III[43] study demonstrated a higher but statistically non-significant rate of mortality owing to indeterminant causes in high-risk patients treated with adjusted-dose warfarin (INR 1.2–1.5) plus aspirin (325 mg) than in those treated with adjusted-dose warfarin (INR 2.0–3.0) alone [3/521 (0.6%) vs 0/523 (0%), respectively; RR 7.00 (95% CI 0.36 to 135.18)] over a mean follow-up period of 1.1 years.[43]

The rates of indeterminate mortality were slightly lower in the SPAF III study[43] than in the AFASAK II study[42] in both the combined therapy group as well as those receiving warfarin alone, despite the methodological differences between these two randomised comparisons.[42,43]

Summary

Combination therapy with ACT and APT did not confer a reduction in mortality from unknown or indeterminant causes over ACT alone in two randomised studies.[42,43]

Other definitions

Bover *et al*.[54] reported non-randomised comparisons for non-cardiac and sudden mortality comparing adjusted-dose acenocoumarol (INR 1.9–2.5) plus three different antiplatelet regimes (triflusal 600 mg, triflusal 300 mg or aspirin 100 mg) with adjusted-dose acenocoumarol (INR 2.0–3.0) alone, over a mean follow-up period of 4.92 years. A specific definition for either outcome was not specified. There were no randomised comparisons identified for this outcome.

More non-cardiac deaths were observed in patients receiving any of the combined therapy regimes (triflusal 600 mg, triflusal 300 mg or aspirin 100 mg) [6/155 (3.9%, 3/120 (2.5%) and 1/34 (2.9%), respectively] than those receiving adjusted-dose acenocoumarol alone [3/265 (1.1%)].[54]

The study reported a higher proportion of sudden deaths in patients receiving a combination of either acenocoumarol plus triflusal 600 mg or acenocoumarol plus aspirin 100 mg than with acenocoumarol alone [4/155 (2.6%), 1/34 (2.9%) vs 3/265 (1.1%), respectively] and a lower rate in those receiving combined acenocoumarol plus triflusal 300 mg than in those receiving acenocoumarol alone [0/120 (0%) vs 3/265 (1.1%), respectively].

Summary

There is no evidence from one non-randomised study for the benefit of combination ACT and APT over ACT alone in the reduction of either non-cardiac or sudden death.[54]

The differences in all-cause mortality reported in the included studies may reflect the methodological differences between these studies discussed above (see *Between-study differences*). In addition, although all-cause mortality was frequently classified as death from non-vascular, indeterminant, unknown or sudden causes, a precise definition of these groupings or subclassifications of mortality was not always supplied in the study reports and/or the definitions may vary between studies for the same subclassification, which may account for some variation in the reported event rates.

Overall summary for mortality (excluding vascular death)

Five studies (three randomised[39,41,42] and two non-randomised[54,69]) demonstrated that there is no evidence that combination therapy with ACT plus APT significantly reduces the risk of all-cause[39,41,42,54,69], non-vascular,[39,42] or non-cardiac[54] mortality, mortality from unknown causes,[42,43] and sudden death[54] compared with ACT alone.

Outcome 9: bleeding

Twenty-seven articles yielded outcome data for bleeding.[39–45,47,51,53,54,56,57,59–65,72,73] Five of these studies in eight articles reported randomised comparisons.[39–45,47] The remaining 19 articles reported non-randomised comparisons of which 14 were primary studies[51,53,54,56,57,59–65,72,73] and five were secondary analyses of the SPORTIF III and SPORTIF V studies.[66–70] Of those that reported non-randomised comparisons, data from four articles are reported in this section,[54,63,69,73] as the others do not report any further relevant data. These other studies are reported in *Appendix 7* except for the study by Akins *et al*.,[67] which has been reported elsewhere in the results section of the report; however, for the outcome of bleeding it does not report the number of bleeding events by therapy group.

Bleeding events were reported either on their own or in conjunction with other events such as embolism and mortality. In those studies that reported bleeding alone, bleeding was classified as major, minor or non-severe, and intracranial. A precise definition of these subclassifications was not always supplied in the study reports and/or the definitions may vary between studies for the same subclassification. The findings of the included studies for each of these subclassifications of bleeding are detailed in *Tables 21* and *22*.

All bleeding outcomes

Three studies[36,41,73] reported all bleeding outcomes, one randomised[41] and two non-randomised[36,73] comparisons.

One randomised comparison[41] in high-risk patients compared adjusted-dose fluindione (INR 2.0–2.6) plus aspirin 100 mg with adjusted-dose fluindione (INR 2.0–2.6) plus placebo. There were significantly more bleeding events in patients receiving combined therapy than in those on fluindione plus placebo [13/76 (17.1%) vs 2/81 (2.5%), respectively; RR 6.93 (95% CI 1.62 to 29.69] during the mean 0.84-year follow-up.

TABLE 21 Randomised comparisons reporting bleeding outcomes

Author, year, study name	Stroke risk, follow-up	ACT + APT, *n*	No. of events/total participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)	RR (95% CI)
[a]Pérez-Gómez *et al.*, 2004, RCT – NASPEAF [39]	High risk,[b] 2.95 years	Adjusted-dose acenocoumarol (INR 1.4–2.4) + triflusal (600 mg), *n* = 223	ICH: 2/223 (0.9)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 247	ICH: 5/247 (2.0)	0.44 (0.09 to 2.26)
			Severe[c]: 12/223 (5.4)		Severe:[c] 13/247 (5.3)	1.02 (0.47 to 2.19)
			Severe – other:[d] 2/223 (0.9)		Severe – other:[d] 5/247 (2.0)	0.44 (0.09 to 2.26)
			Non-severe: 20/223 (8.9)		Non-severe: 18/247 (7.3)	1.23 (0.67 to 2.27)
	Intermediate risk,[e] 2.6 years	Adjusted-dose acenocoumarol (INR 1.25–2.0) + triflusal (600 mg), *n* = 222	ICH: 1/222 (0.5)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 232	ICH: 4/232 (1.7)	0.48 (0.05 to 4.21)
			Severe:[c] 5/222 (2.3)		Severe:[c] 10/232 (4.3)	0.52 (0.18 to 1.50)
			Severe – other:[d] 1/222 (0.5)		Severe – other:[d] 5/232 (2.2)	0.21 (0.02 to 1.77)
			Non-severe: 16/222 (7.2)		Non-severe: 15/232 (6.5)	1.11 (0.56 to 2.20)
Lidell *et al.*, 2003[40]	Risk NR, 22 days	Adjusted-dose warfarin (INR 2.0–3.0) + clopidogrel (75 mg), *n* = 20	Minor: 0/20 (0)	Adjusted-dose warfarin (INR 2.0–3.0) + placebo, *n* = 23	Minor: 5/23 (21.8)	0.10 (0.01,1.77)
Lechat *et al.*, 2001 RCT – FFAACS[41]	High risk,[f] 0.84 years	Adjusted-dose fluindione (INR 2.0–2.6) + aspirin (100 mg), *n* = 76	Severe: 3/76 (3.9)	Adjusted-dose fluindione (INR 2.0–2.6) + placebo, *n* = 81	Severe: 1/81 (1.2)	3.19 (0.34 to 30.07)
			Non-severe: 10/76 (13.2)		Non-severe: 1/81 (1.2)	10.66 (1.39 to 81.28)
			All: 13/76 (17.1)		All: 2/81 (2.5)	6.93 (1.62 to 29.69)

Author, year, study name	Stroke risk, follow-up	ACT + APT, *n*	No. of events/total participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)	RR (95% CI)
[g]Gullov *et al.*, 1998 RCT – AFASAK II[42]	Risk NR, 3.5 years	Fixed-dose warfarin (1.25 mg) + aspirin (300 mg), *n* = 171	ICH: 0/171 (0)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 170	ICH: 2/170 (1.2)	0.19 (0.01 to 4.11)
					Major:[h] 4/170 (2.4)	0.25 (0.03 to 2.20)
			Major:[h] 1/171 (0.6)		Minor:42/170 (24.7)	0.66 (0.43 to 1.02)
				Fixed-dose warfarin (1.25 mg), *n* = 167	ICH: 1/167 (0.6)	0.33 (0.13 to 7.94)
			Minor: 28/171 (16.4)		Major:[h] 3/167 (1.8)	0.33 (0.03 to 3.09)
					Minor: 21/167 (12.6)	1.30 (0.77 to 2.19)
SPAF investigators, 1996 RCT – SPAF III[43]	High risk,[i] 1.1 years	Adjusted-dose warfarin (INR 1.2–1.5) + aspirin (325 mg), *n* = 521	ICH: 5/521 (0.9)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 523	ICH: 3/523 (0.6)	1.67 (0.40 to 6.96)
			Major:[h] 13/521 (2.5)		Major:[h] 12/523 (2.3)	1.08 (0.50 to 2.36)
			Minor: 6/521 (1.2)		Minor: 4/523 (0.8)	1.5 (0.43 to 5.30)

GI, gastrointestinal; NR, not reported; NVAF, non-valvular atrial fibrillation.

a Supported by *n* = 2 subgroup analyses[44,45] that reported duplicate data and are not reported in this table.

b Either NVAF with prior embolism or those with mitral stenosis with or without prior embolism.

c Includes fatal bleed, GI bleed and ICH.

d Does not include GI bleed or ICH.

e NVAF with no embolism at baseline.

f Presence of at least one of history of TE (TIA, non-disabling ischaemic stroke or peripheral embolism) or aged > 65 years, and at least one of history of hypertension (systolic arterial pressure of > 160 mmHg or diastolic arterial pressure > 90 mmHg); recent episode (< 3 months previously) of congestive HF or alteration in left ventricular function (echocardiographic left ventricular shortening fraction< 25% or LVEF< 40% within 3 months before study inclusion).

g Supported by an analysis[47] that reported duplicate data, not reported in this table.

h Includes intracerebral haemorrhagic events.

i Presence of at least one of the following: impaired left ventricular function manifested by recent (≤100 days) congestive HF, or fractional shortening ≤25% by M-mode echocardiography; systolic blood pressure > 160 mmHg at study entry; prior ischaemic stroke, TIA or SE (i.e. prior TE); female sex or aged > 75 years.

One non-randomised comparison (PETRO[73]) compared combinations of different doses of dabigatran (50, 150 and 300 mg) plus different regimes of aspirin (81 and 325 mg) with dabigatran alone (50 mg, 150 mg, 300 mg). Higher proportions of bleeding were found in patients receiving combination therapy at all doses of dabigatran plus aspirin than in those receiving dabigatran alone (see *Table 22*). A higher proportion of bleeding events were observed in patients on the combination therapy of dabigatran 50 mg plus either aspirin 81 mg or 325 mg [2/21 (9.5%) and 3/27 (11.1%), respectively] than in those receiving dabigatran 50 mg alone [2/59 (3.4%)]. A higher proportion of events were observed in patients on the combined therapy of dabigatran 150 mg plus either aspirin 81 or 325 mg [8/36 (22.2%), 7/33 (21.2%), respectively] than in those receiving dabigatran 150 mg alone [15/100 (15%)]. A higher proportion of patients on the combined therapy of dabigatran 300 mg plus either aspirin 81 or 325 mg [11/34 (32.4%), 14/30 (46.7%), respectively] suffered a bleeding event than in those receiving dabigatran 300 mg alone [14/105 (13.3%)] during a mean follow-up period of 22 weeks. Randomised comparisons for dabigatran plus an antiplatelet agent compared with dabigatran alone were not identified.

Hansen *et al*.[63] reported registry data comparing warfarin (INR target not stated) in combination with either aspirin (dose not stated) or clopidogrel (dose not stated) or both clopidogrel and aspirin (dose not stated), with warfarin alone (dose not stated). The rate of bleeding was similar among patients receiving warfarin plus aspirin or warfarin alone [1209/18,345 (6.6%) vs 3642/50,919 (7.2%], respectively), although the rate of bleeding was slightly lower in patients receiving either warfarin plus clopidogrel (69/1430 (4.8%)] or triple therapy [64/1261 (5.1%)] than in those receiving warfarin alone [3642/50,919 (7.2%)]. However, the use of an antiplatelet agent is confounded by indication and given that bleeding is a contraindication to ATT-only patients felt to be at low risk of bleeding may have been given combination therapy in this non-randomised comparison.

Summary

There is conflicting evidence regarding the effect of combination ACT plus APT compared with ACT alone on the risk of all bleeding. Two studies (one randomised[41] and one non-randomised[73]) demonstrated higher rates of overall bleeding with some combination therapy (fluindione plus aspirin[41] and dabigatran plus aspirin[73]) over ACT alone, whereas one other non-randomised study[63] found similar levels of bleeding with combination therapy (warfarin plus aspirin or clopidogrel) compared with ACT alone.[54]

Major (or severe) haemorrhage

Four randomised comparisons[39–43] and three non-randomised comparisons[54,69,73] reported data on major (or severe) haemorrhage.

The AFASAK II[42] study defined major haemorrhage as fatal, life-threatening, or potentially life-threatening, requiring surgical treatment or blood transfusion. All life-threatening bleeds were confirmed from hospital records. The SPAF III[43] study defined major haemorrhage according to the Landfeld criteria, i.e. overt bleeding that was fatal, life-threatening, potentially life-threatening, or acute or subacute leading to reoperation or moderate or severe blood loss.[93] The NASPEAF[39] study defined severe haemorrhage as requiring hospital admission, blood transfusion, or surgery. The FFAACS study defined severe haemorrhage as needing treatment (including transfusion) or hospitalisation.[41] These definitions are broadly comparable and are considered equivalent for the purposes of this review.

The AFASAK II[42] and SPAF III[43] studies reported randomised comparisons for major haemorrhage comparing different regimes of combined warfarin plus aspirin with warfarin alone. The findings of these studies are reported in *Table 21*.

The AFASAK II[42] study reported very low event rates with a non-significant difference in rates of major bleeding between combined fixed-dose warfarin (1.25 mg daily) plus aspirin (300 mg daily) and adjusted-dose warfarin (INR 2.0–3.0) alone [1/171 (0.6%) vs 4/170 (2.4%), respectively, RR 0.25, 95% CI 0.03 to 2.20] or fixed-dose warfarin (1.25 mg daily) alone [1/171 (0.6%) vs 3/167 (1.8%), respectively, RR 0.33, 95% CI 0.03 to 3.09] during the mean 3.5 years of follow-up. The risk profile of the patients enrolled in this study[42] was not specified.

The SPAF III[43] study reported very similar rates of major bleeding in patients on either adjusted-dose warfarin (INR 1.2–1.5) plus aspirin (325 mg daily) or adjusted-dose warfarin (INR 2.0–3.0) alone in high-risk patients with AF [13/521 (2.5%) vs 12/523 (2.3%), respectively, RR 1.08, 95% CI 0.5 to 2.36] during the mean 1.1-year follow-up period.[43]

Flaker *et al*.[69] reported non-randomised data on a pooled analysis of the SPORTIF III and V studies comparing combined adjusted-dose warfarin (INR 2.0–3.0) plus aspirin (100 mg) with adjusted-dose warfarin alone (INR 2.0–3.0) (*Table 22*). Higher rates of major bleeding were reported in the combined therapy group than in the warfarin alone group [25/481 (5.2%) vs 100/3172 (3.2%), respectively] during the mean 16.5-month follow-up.

There were small differences in the event rates of major bleeding in the two RCTs. In the combination therapy arms of the randomised comparisons, the rate of major bleeding was higher in the SPAF III[43] study than in the AFASAK II[42] study [13/521 (2.5%) vs 1/171 (0.6%), respectively], and much lower than the rate of major bleeding with combination warfarin and aspirin therapy in the SPORTIF III and V[69] studies [25/481 (5.2%)]. However, rates were similar in those receiving warfarin alone in the SPAF III study,[43] 12 out of 523 patients (2.3%) to those on either adjusted-dose warfarin (INR 2.0–3.0) alone or those receiving fixed-dose warfarin (1.25 mg) alone [4/170 (2.4%) and 3/167 (1.8%), respectively] in the AFASAK II study,[42] and adjusted-dose warfarin alone in SPORTIF III and V[69] studies [100/3172 (3.2%)]. Of note is the fact that the SPAF III[43] and AFASAK II[42] studies included intracerebral haemorrhage events in their definitions of major bleeding; however, the SPORTIF studies[69] include both ICH as well as fatal bleed in the total rate of major haemorrhage. This might also explain the differences in the event rates between these studies in addition to the methodological heterogeneity discussed in detail above (see *Between-study differences*).

The NASPEAF trial[39] reported very similar major bleeding event rates in patients on combined adjusted-dose acenocoumarol (INR 1.4–2.4) plus triflusal (600 mg) and those on adjusted-dose acenocoumarol (INR 2.0–3.0) alone in high-risk patients during the median 2.6-year follow-up [12/223 (5.4%) vs 13/247 (5.3%), respectively, RR 1.02 95% CI 0.47 to 2.19]. The rate of major bleeding was lower, but not significantly so, among intermediate-risk patients receiving combined adjusted-dose acenocoumarol (INR 1.2–2.0) and triflusal (600 mg) than in those receiving adjusted-dose acenocoumarol (INR 2.0–3.0) alone during a median 2.9-year follow-up [5/222 (2.3%) vs 10/232 (4.3%), respectively, RR 0.52, 95% CI 0.18 to 1.50].[39]

Bover *et al*.[54] reported data comparing combined adjusted-dose acenocoumarol (INR 1.9–2.5) in combination with three antiplatelet regimes (triflusal 600 mg and 300 mg, aspirin 100 mg) to adjusted-dose acenocoumarol (INR 2.0–3.0) alone. Higher rates of bleeding were observed in patients on combined acenocoumarol plus aspirin [7/34 (20.6%)] and lower rates in those on combined acenocoumarol plus triflusal 600 mg [10/155 (6.5%)] or combined acenocoumarol plus triflusal 300 mg [6/120 (5.0%)] than in those on acenocoumarol alone [35/265 (12.1%)] during the mean 4.92 years of follow-up.[54] However, the population in this study was derived from a cohort of another RCT (see *Between-study differences*).

The FFAACS study[41] reported higher, but not significantly different, rates of major bleeding with combined adjusted-dose fluindione (INR 2.0–2.6) plus aspirin (100 mg) than with adjusted-dose fluindione (INR 2.0–2.6) plus placebo in high-risk patients during the mean 0.84-year follow-up [3/76 (3.9%) vs 1/81 (1.2%), respectively, RR 3.19, 95% CI 0.34 to 30.07].[41]

There was no non-randomised evidence for this comparison identified for major bleeding.

Flaker *et al*.[69] reported data on a pooled analysis of the SPORTIF III and V studies comparing combined ximelagatran (36 mg twice daily) and aspirin (≤ 100 mg) with ximelagatran (36 mg twice daily) alone. Lower rates of major haemorrhage were reported in patients on combination therapy than in those on ximelagatran alone [2/531 (0.4%) vs 78/3120 (2.5%), respectively] during the 16.5-month follow-up.

The PETRO study[73] reported no major bleeding events in patients on dabigatran 50 mg or 150 mg (in combination with aspirin or given alone). However, a higher proportion of patients on combined therapy of dabigatran 300 mg plus either aspirin 81 mg or 325 mg [1/34 (2.9%), 3/30 (10%) respectively] suffered a major bleeding event than those on dabigatran 300 mg alone [0/105 (0%)] during a mean follow-up period of 22 weeks.

Summary

There is conflicting evidence regarding the effect of combination ACT plus APT compared with ACT alone on the risk of major bleeding. Four randomised studies reported relatively low event rates and demonstrated no significant increase in the risk of major bleeding with combination therapy compared with ACT alone.[39,41–43] Three non-randomised studies reported inconsistent data, with two demonstrating higher rates of major bleeding with some combination therapy (VKAs plus aspirin)[54,69] over ACT alone, and lower bleeding rates with other combined therapy (VKA plus triflusal[54] or ximelagatran plus aspirin[69]), whereas the other study reported an increased risk of major bleeding only with the highest dose of ACT plus APT compared with ACT alone.[73]

Intracranial haemorrhage

Three randomised comparisons[39,42,43] and no non-randomised comparisons reported data on ICH. None of the studies included a definition of ICH.

The AFASAK II[42] and SPAF III[43] studies reported randomised comparisons for ICH comparing different regimes of combined warfarin plus aspirin to warfarin alone. The findings of these studies are reported in *Table 21*.

The AFASAK II[42] study reported very low event rates with a non-significant difference in rates of intracranial bleeding between combined fixed-dose warfarin (1.25 mg daily) plus aspirin (300 mg daily) and adjusted-dose warfarin (INR 2.0–3.0) alone [0/171 (0%) vs 2/170 (1.2%), respectively, RR 0.19, 95% CI 0.01 to 4.11] or fixed-dose warfarin (1.25 mg daily) alone [0/171, (0%) vs 1/167 (0.6%), respectively, RR 0.33, 95% CI 0.13 to 7.94] during the median 3.5 years of follow-up. The risk profile of the patients enrolled in this study was not specified.[42]

The SPAF III[43] study reported very similar rates of ICH in patients on either adjusted-dose warfarin (INR 1.2–1.5) plus aspirin (325 mg daily) or adjusted-dose warfarin (INR 2.0–3.0) alone in high-risk patients with AF [5/521 (0.9%) vs 3/523 (0.6%), respectively, RR 1.67, 95% CI 0.4 to 6.96] during the mean 1.1-year follow-up period.[43]

The rate of ICH was very low and similar in both of these RCTs. In the combined therapy arm, the rate of ICH was 0.9% (5/521) in the SPAF III[43] study compared with 0% in the AFASAK II study.[42] Rates of ICH were similar in those receiving either fixed- or adjusted-dose warfarin in the AFASAK II[42] study [2/170 (1.2%) and 1/167 (0.6%), respectively] and adjusted-dose warfarin in the SPAF III study [3/523 (0.6%)]. The difference in the rates may be explained by methodological heterogeneity between the included studies (see *Between-study differences*).

The NASPEAF trial[39] reported low event rates with non-significant differences in rates of ICH between combined adjusted-dose acenocoumarol (INR 1.4–2.4) plus triflusal (600 mg), and adjusted-dose acenocoumarol (INR 2.0–3.0) alone [2/223 (0.9%) vs 5/247 (2.0%), respectively, RR 0.44, 95% CI 0.09 to 2.26] in high-risk patients during the median 2.6-year follow-up, or combined adjusted-dose acenocoumarol (INR 1.2–2.0) plus triflusal (600 mg) compared with adjusted-dose acenocoumarol (INR 2.0–3.0) alone [1/222 (0.5%) vs 4/232 (1.7%), respectively, RR 0.48, 95% CI 0.05 to 4.21] in intermediate-risk patients during a median 2.9-year follow-up.[39]

Summary

The rate of ICH reported in three randomised studies[39,42,43] was very low and there was no evidence of a significantly increased risk of ICH with combination therapy over ACT alone.

Minor (or non-severe) bleeding

Five randomised comparisons[39–43] and no non-randomised comparisons reported data on minor or non-severe bleeding. Definitions for minor bleeding were not clearly specified in these studies.

The AFASAK II[42] and SPAF III[43] studies reported randomised comparisons for minor bleeding comparing different regimes of combined warfarin plus aspirin with warfarin alone. The findings of these studies are reported in *Table 21*.

The AFASAK II[42] study reported a non-significant difference in rates of minor bleeding when combined fixed-dose warfarin (1.25 mg daily) plus aspirin (300 mg daily) was compared with either adjusted-dose warfarin (INR 2.0–3.0) alone [28/171 (16.4%) vs 42/170 (24.7%), respectively, RR 0.66, 95% CI 0.43 to 1.02] or fixed-dose warfarin (1.25 mg daily) alone [28/171 (16.4%) vs 21/167 (12.6%), respectively, RR 1.30, 95% CI 0.77 to 2.19] during the median 3.5 years of follow-up. The risk profile of the patients enrolled in this study[42] was not specified.

The SPAF III[43] study also reported similar rates of minor haemorrhage in patients on either adjusted-dose warfarin (INR 1.2–1.5) plus aspirin (325 mg daily) or adjusted-dose warfarin (INR 2.0–3.0) alone in high-risk patients with AF [6/521 (1.2%) vs 4/523 (0.8%), respectively, RR 1.5 95% CI 0.43 to 5.30] during the mean 1.1-year follow-up period.[43]

The rates of minor bleeding were much higher in the AFASAK II[42] study than in the SPAF III[43] study for both the combination therapy [28/171 (16.4%) vs 6/521 (1.2%), respectively] and warfarin-alone arms [adjusted-dose warfarin alone 42/170 (24.7%) vs 4/523 (0.8%), respectively] and 21/167 (12.6%) for fixed-dose warfarin alone in the AFASAK II[42] study arms.

There was no non-randomised evidence reported for this comparison/outcome combination.

Lidell *et al*.[40] reported a non-significant difference in rates of minor bleeding between patients on either combined adjusted-dose warfarin (INR 2.0–3.0) plus clopidogrel (75 mg), or adjusted-dose warfarin (2.0–3.0) plus placebo [0/20 (0%) vs 5/23 (21.8%), respectively, RR 0.10, 95% CI 0.01 to 1.17] during the mean follow-up of 22 days.

There was no non-randomised evidence for this comparison identified for minor bleeding.

TABLE 22 Non-randomised comparisons reporting bleeding outcomes

Author, year, study name	Stroke risk, follow-up	ACT + APT, *n*	No. of events/total participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)
[a]Hansen *et al.*, 2010[63]	Risk NR, 3.3 years	Warfarin + aspirin, *n* = 18,345	All: 1209/18,345 (6.6)	Warfarin, *n* = 50,919	All: 3642/50,919 (7.2)
		Warfarin + clopidogrel, *n* = 1430	All: 69/1430 (4.8)		
		Warfarin + aspirin + clopidogrel, *n* = 1261	All: 64/1261 (5.1)		
[b]Bover *et al.*, 2009[54]	Risk NR, 4.92 years	Adjusted-dose acenocoumarol (INR 1.9–2.5) + triflusal (600 mg), *n* = 155	Severe:[c] 10/155 (6.5) Fatal: 0/155 (0) GI: 8/155 (5.2)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 265	Severe:[c] 32/265 (12.1) Fatal: 7/265 (2.6) GI: 6/265 (2.3)
		Adjusted-dose acenocoumarol (INR 1.9–2.5) + triflusal (300 mg), *n* = 120	Severe:[c] 6/120 (5.0) Fatal: 1/120 (0.8) GI: 5/120 (4.2)		
		Adjusted-dose acenocoumarol (INR 1.9–2.5) + aspirin (100 mg), *n* = 34	Severe:[c] 7/34 (20.6) Fatal: 2/34 (5.9) GI: 0/34 (0)		
Ezekowitz *et al.*, 2007, RCT – PETRO[73]	≥ 1 stroke risk criteria,[d] 22 weeks	Dabigatran (50 mg) + aspirin (81 mg), *n* = 21	Major: 0/21 (0) Clinical relevant + major: 1/21 (4.8) All:[e] 2/21 (9.5)	Dabigatran (50 mg), *n* = 59	Major: 0/59 (0) Clinical relevant + major: 0/59 (0) All:[e] 2/59 (3.4)
		Dabigatran (50 mg) + aspirin (325 mg), *n* = 27	Major: 0/27 (0) Clinical relevant + major: 1/27 (3.7) All:[e] 3/27 (11.1)		
		Dabigatran (150 mg) + aspirin (81 mg), *n* = 36	Major: 0/36 (0) Clinical relevant + major: 2/36 (5.6) All:[e] 8/36 (22.2)	Dabigatran (150 mg), *n* = 100	Major: 0/100 (0) Clinical relevant + major: 9/100 (9.0) All:[e] 15/100 (15.0)
		Dabigatran (150 mg) + aspirin (325 mg), *n* = 33	Major: 0/33 (0) Clinical relevant + major: 2/33 (6.1) All:[e] 7/33 (21.2)		
		Dabigatran (300 mg) + aspirin (81 mg), *n* = 34	Major: 1/34 (2.9) Clinical relevant + major: 5/34 (14.7) All:[e] 11/34 (32.4)	Dabigatran (300 mg), *n* = 105	Major: 0/105 (0) Clinical relevant + major: 6/105 (5.7) All:[e] 14/105 (13.3)
		Dabigatran (300 mg) + aspirin (325 mg), *n* = 30	Major: 3/30 (10.0) Clinical relevant + major: 6/30 (20.0) All:[e] 14/30 (46.7)		

TABLE 22 Non-randomised comparisons reporting bleeding outcomes (*continued*)

Author, year, study name	Stroke risk, follow-up	ACT + APT, *n*	No. of events/total participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)
[f]Flaker *et al.*, 2006[69]	High risk,[g] 16.5 months	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (≤100 mg), *n* = 481	Major:[h] 25/481 (5.2) Major/minor: 251/481 (52.2)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 3172	Major:[h] 100/3172 (3.2) Major/minor: 1199/3172 (37.8)
		Ximelagatran (36 mg b.i.d.) + aspirin (≤100 mg), *n* = 531	Major:[h] 2/531 (0.4) Major/minor: 202/531 (38.0)	Ximelagatran (36 mg b.i.d.), *n* = 3120	Major:[h] 78/3120 (2.5) Major/minor: 1013/3120 (32.5)

b.i.d., dose administered twice daily; GI, gastrointestinal; NR, not reported.

a Study does not report doses of antithrombotic therapies used.

b Longitudinal follow-up of randomised cohort of NASPEAF study[39] with additional participants.

c Includes fatal bleed, GI bleed and ICH.

d All patients with ST-segment elevation MI and undergoing PCI.

e Also includes clinically relevant, fatal and major bleed.

f Also reports bleeding outcomes according to individual sites for warfarin or ximelagatran + aspirin vs warfarin or ximelagatran (alone).

g At least one of the following risk factors: previous stroke/TIA/SE, hypertension, left ventricular dysfunction (ejection fraction <40% or symptomatic systolic or diastolic HF), aged ≥75 years or aged ≥65 years with known coronary disease/diabetes mellitus.

h Also includes ICH and fatal bleed.

The NASPEAF study[39] reported non-significant differences in rates of non-severe haemorrhage between combined adjusted-dose acenocoumarol (INR 1.4–2.4) plus triflusal (600 mg) and adjusted-dose acenocoumarol (INR 2.0–3.0) alone in high-risk patients during the median 2.6-year follow-up [20/223 (8.9%) vs 18/247 (7.3%), respectively, RR 1.23, 95% CI 0.67 to 2.27] or combined adjusted-dose acenocoumarol (INR 1.2–2.0) plus triflusal (600 mg) compared with adjusted-dose acenocoumarol (INR 2.0–3.0) alone [16/222 (7.2%) vs 15/232 (6.5%), respectively, RR 1.11, 95% CI 0.56 to 2.20] in intermediate-risk patients during a median follow-up of 2.9 years.

There was no non-randomised evidence for this comparison identified for minor bleeding.

The FFAACS trial[41] reported a significant difference in rates of non-severe bleeding, with more events in patients on combined adjusted-dose fluindione (INR 2.0–2.6) plus aspirin (100 mg), than in those on adjusted-dose fluindione (INR 2.0–2.6) plus placebo in high-risk patients during the mean 0.84-year follow-up [10/76 (13.2%) vs 1/81 (1.2%), respectively, RR 10.66, 95% CI 1.39 to 81.28].

There was no non-randomised evidence for this comparison identified for minor bleeding.

The differences in bleeding outcomes reported in the included studies may reflect the methodological differences between these studies, which are discussed in detail above (*Between-study differences*). Various definitions of major bleeding were used across included studies (although these were considered broadly comparable for the purposes of this review), and subclassifications of bleeding varied between studies and were not always clearly defined. In addition, the likelihood of bleeding is reduced when the INR is <3.0 and, therefore, studies using INR targets <3.0[39,42,43,54] in either the intervention and/or comparator arms may have resulted in few bleeding events. Furthermore, only four studies[39,40,43,54] (three randomised[39,40,43] and one non-randomised[54]) reported TTR for ACT plus APT and ACT alone. TTR

is associated with the incidence of bleeding events; when TTR is better (≥70%) the likelihood of adverse bleeding events is significantly reduced.[94] Therefore, differences in the TTR may help to explain differences in the bleeding event rates reported. Moreover, in the combined therapy group in the non-randomised studies, those patients with a high risk of bleeding may not have received additional APT and, therefore, potential confounding by indication may also account for differences in the bleeding rates reported.

Summary

Four randomised studies[39,40,42,43] demonstrated no significant increased risk in minor or non-severe bleeding with combination therapy compared with anticoagulation alone, whereas another small randomised study[41] reported a significant increase in the risk of minor/non-severe bleeding with combined therapy.

Outcome 10: patient quality of life

Of the included studies, no study was identified that reported quality-of-life outcome for the comparisons of interest.

Outcome 11: major adverse events (all-cause mortality, non-fatal myocardial infarction and stroke) and other composite outcomes

No study was identified that reported major adverse events comprising all-cause mortality, non-fatal MI and stroke. Six articles[39,41,43–45,54] reported other composite events, which included combined end points consisting of two or more previously reported outcomes. Three studies (in five articles[39,41,43–45]) reported randomised comparisons, and one study[54] reported non-randomised comparisons for various composite end points. The findings of these studies are reported in *Table 23* and *24*, respectively.

Severe bleeding, non-fatal stroke, transient ischaemic attack, systemic embolism and vascular death

The NASPEAF study reported a randomised comparison on the composite outcome of severe bleeding, non-fatal stroke, TIA, SE and vascular death comparing adjusted-dose acenocoumarol (INR 1.4–2.4) plus triflusal (600 mg) with acenocoumarol alone (INR 2.0–3.0) in high-risk patients, and the combination of adjusted-dose acenocoumarol (INR 1.2–2.0) plus triflusal (600 mg) with acenocoumarol alone (INR 2.0–3.0) in intermediate-risk patients. A lower but statistically non-significant rate of the composite end point occurred in the combined therapy group than in those receiving anticoagulant alone in the high-risk patients [22/223 (9.9%) vs 34/247 (13.8%), respectively, RR 0.72 (95% CI 0.43 to 1.19)] during a median follow-up of 2.95 years. A similar trend was observed in the intermediate-risk group, for which the combination therapy arm demonstrated a lower composite event rate than the acenocoumarol-alone arm [8/222 (3.6%) vs 21/232 (9.1%) respectively, RR 0.40 (95% CI 0.18 to 0.88)] after a median follow-up of 2.6 years (see *Table 23*).

No other study was identified that evaluated this composite outcome.

Embolism, stroke, acute myocardial infarction and vascular death

The NASPEAF study[39] reported a randomised comparison on the composite outcome of embolism, stroke, AMI and vascular death.

A lower but statistically non-significant rate of the composite end point was observed in patients receiving combined therapy than in those on anticoagulant alone, in both the high-risk patients [13/223 (5.8%) vs 25/247 (10.1%), respectively, RR 0.58 (95% CI 0.30 to 1.10)] during a median follow-up of 2.95 years, as well as the intermediate-risk patients [4/222 (1.8%) vs 8/232 (3.4%), respectively, RR 0.52

TABLE 23 Randomised comparisons reporting composite events as outcomes

Author, year	Stroke risk, follow-up	ACT + APT, *n*	No. of events/participants in ACT + APT arm (%)	ACT (alone or ACT + placebo), *n*	No. of events/total participants in ACT arm (%)	RR (95% CI)
[a]Pérez-Gómez *et al.*, 2004, RCT – NASPEAF[39]	High risk,[b] 2.95 years	Adjusted-dose acenocoumarol (INR 1.4–2.4) + triflusal (600 mg), *n* = 223	Severe bleeding, non-fatal stroke, TIA, SE and vascular death: 22/223 (9.9)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 247	Severe bleeding, non-fatal stroke, TIA, SE and vascular death: 34/247 (13.8)	0.72 (0.43 to 1.19)
			Embolism, stroke, AMI and vascular death: 13/223 (5.8)		Embolism, stroke, AMI and vascular death: 25/247 (10.1)	0.58 (0.30 to 1.10)
			Non-fatal stroke, TIA, SE, and vascular death: 14/223 (6.3)		Non-fatal stroke, TIA, SE, and vascular death: 29/247 (11.7)	0.53 (0.29 to 0.99)
	Intermediate risk,[c] 2.6 years	Adjusted-dose acenocoumarol (INR 1.25–2.0) + triflusal (600 mg), *n* = 222	Severe bleeding, non-fatal stroke, TIA, SE and vascular death: 8/222 (3.6)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 232	Severe bleeding, non-fatal stroke, TIA, SE and vascular death: 21/232 (9.1)	0.40 (0.18 to 0.88)
			Embolism, stroke, AMI and vascular death: 4/222 (1.8)		Embolism, stroke, AMI and vascular death: 8/232 (3.4)	0.52 (0.16 to 1.71)
			Non-fatal stroke, TIA, SE, and vascular death: 5/222 (2.3)		Non-fatal stroke, TIA, SE, and vascular death: 15/232 (16.5)	0.35 (0.13 to 0.94)
Lechat *et al.*, 2001, RCT – FFAACS[41]	High risk,[d] 0.82 years	Adjusted-dose fluindione (INR 2.0–2.6) + aspirin (100 mg), *n* = 76	SE, death: 5/76 (6.6)	Adjusted-dose fluindione (INR 2.0–2.6) + placebo, *n* = 81	SE and death: 2/81 (2.5)	2.66 (0.53 to 13.33)
SPAF investigators, 1996 RCT – SPAF III[43]	High risk,[e] 1.1 years	Adjusted-dose warfarin (INR 1.2–1.5) + aspirin (325 mg), *n* = 521	Stroke, SE, vascular death: 66/521 (12.7)	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 523	Stroke, SE and vascular death: 37/523 (7.1)	1.79 (1.22 to 2.63)

NVAF, non-valvular atrial fibrillation.

a Supported by *n* = 2 subgroup analyses[44,45] that reported duplicate data and were not reported in this table.

b Either NVAF with prior embolism or those with mitral stenosis with and without prior embolism.

c NVAF with no embolism at baseline.

d Presence of at least one of history of TE (TIA, non-disabling ischaemic stroke or peripheral embolism) or aged > 65 years, and at least one of history of hypertension (systolic arterial pressure of > 160 mmHg or diastolic arterial pressure of > 90 mmHg); recent episode (< 3 months previously) of congestive HF or alteration in left ventricular function (echocardiographic left ventricular shortening fraction of < 25% or LVEF of < 40% within 3 months before study inclusion).

e Presence of at least one of the following: impaired left ventricular function manifested by recent (≤ 100 days) congestive heart disease or fractional shortening of ≤ 25% by M-mode echocardiography; systolic blood pressure of > 160 mmHg at study entry: prior ischaemic stroke, TIA or SE (i.e. prior TE); female sex or aged > 75 years.

(95% CI 0.16 to 1.71)] after a median follow-up of 2.6 years (see *Table 23*). No other study reporting a composite end point of embolism, stroke, AMI and vascular death was identified.

Non-fatal stroke, transient ischaemic attack, systemic embolism and vascular death

The NASPEAF study[39] reported a lower rate of non-fatal stroke, TIA, SE and vascular death as a composite end point in patients receiving combined therapy than in those on anticoagulant alone, in both the high-risk patients [14/223 (6.3%) vs 29/247 (11.7%), respectively, RR 0.53 (95% CI 0.29, 0.99)] during a median follow-up of 2.95 years, as well as the intermediate-risk patients [5/222 (2.3%) vs 15/232 (16.5%), respectively, RR 0.35 (95% CI 0.13 to 0.94)] after a median follow-up of 2.6 years (see *Table 23*).

No other study reporting a composite end point of embolism, stroke, AMI and vascular death was identified.

Systemic embolism and death

The FFAACS[41] study reported randomised data comparing adjusted-dose fluindione (INR 2.0–2.6) plus aspirin 100 mg to adjusted-dose fluindione (INR 2.0–2.6) alone. Although not significantly different, composite events of SE and death were reported among patients receiving combination therapy compared with patients receiving fluindione alone [5/76 (6.6%) vs 2/81 (2.5%), respectively, RR 2.66 (95% CI 0.53 to 13.33)] during a mean 0.84-year follow-up (see *Table 23*).

No other study reporting the composite end point of SE and death was identified.

Stroke, systemic embolism and vascular death

The SPAF III study[43] reported a randomised comparison for rates of the composite outcome of stroke, SE and vascular death comparing adjusted-dose warfarin (INR 1.2–1.5) plus aspirin (325 mg) with adjusted-dose warfarin (target INR 2.0–3.0) alone in high-risk patients with AF. A significantly higher incidence of the composite end point was observed in the combined therapy arm than in those receiving warfarin alone [66/521 (12.7%) vs 37/523 (7.1%), respectively, RR 1.79 (95% CI 1.22 to 2.63)] over a mean follow-up period of 1.1 years.[43]

No other studies reporting data on this composite end point were identified.

Ischaemic events (all)

Bover *et al*.[54] reported non-randomised data on the composite outcome of all ischaemic events comparing adjusted-dose acenocoumarol (INR 1.9–2.5) plus three different regimes of APT (triflusal 600 mg or 300 mg, aspirin 100 mg) with adjusted-dose acenocoumarol alone (INR 2.0–3.0) over a mean follow-up period of 4.92 years (see *Table 24*).

A combination of adjusted-dose acenocoumarol (target INR 1.9–2.5) with triflusal 600 mg or aspirin 100 mg demonstrated fewer ischaemic events [4/155 (2.6%) and 0/34 (0%), respectively] than acenocoumarol alone [22/265 (8.3%)]. However, patients receiving acenocoumarol plus triflusal 300 mg demonstrated more ischaemic events than those on acenocoumarol alone [11/120 (9.2%) vs 22/265 (8.3%), respectively] (see *Table 23*).

There were no randomised comparisons identified that reported a composite end point of all ischaemic events.

Stroke, systemic/coronary ischaemic events, acute myocardial infarction and mortality

Bover *et al*.[54] reported lower rates of the composite end point of stroke, systemic/coronary ischaemic events, AMI and mortality in patients on combined therapy of acenocoumarol with either triflusal 600 mg, triflusal 300 mg or aspirin 100 mg [9/155 (5.8%), 12/120 (10%) and 3/34 (8.8%), respectively]

TABLE 24 Non-randomised comparisons reporting composite events as outcomes

Author, year	Stroke risk, follow-up	ACT + APT, *n*	No. of events/total participants in ACT + APT group (%)	ACT (alone), *n*	No. of events/total participants in ACT group (%)
Bover *et al.*, 2009[54]	Stroke risk NR, 4.92 years	Adjusted-dose acenocoumarol (INR 1.9–2.5) + triflusal (600 mg), *n* = 155	Ischaemic events (all): 4/155 (2.6) Stroke,[a] systemic/coronary ischaemic events, AMI and mortality: 9/155 (5.8)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 265	
		Adjusted-dose acenocoumarol (INR 1.9–2.5) + triflusal (300 mg), *n* = 120	Ischaemic events (all): 11/120 (9.2) Stroke,[a] systemic/coronary ischaemic events, AMI and mortality: 12/120 (10)		Ischaemic events – all: 22/265 (8.3) Stroke,[a] systemic/coronary ischaemic events, AMI and mortality: 37/265 (13.9)
		Adjusted-dose acenocoumarol (INR 1.9–2.5) + aspirin (100 mg), *n* = 34	Ischaemic events (all): 0/34 (0) Stroke,[a] systemic/coronary ischaemic events, AMI and mortality: 3/34 (8.8)		

NR, not reported.
a Ischaemic and haemorrhagic stroke.

than those on acenocoumarol alone [37/265 (13.9%)] over a mean follow-up period of 4.92 years. Of note is the fact that this study consisted of the majority of patients enrolled from another RCT (see *Between-study differences*).

There were no randomised comparisons identified that reported the composite end point of stroke, systemic/coronary ischaemic events, AMI and mortality.

The differences in major adverse event outcomes reported in the included studies may reflect the methodological differences between these studies discussed in detail above (*Between-study differences*). Different combinations of major adverse events were examined in composite events in each of the included studies and, therefore, it is not possible to compare across studies.

Summary

Although lower major adverse event rates were observed in three studies[39,41,54] (two randomised[39,41] and one non-randomised[54]) with combination therapy for the composite end points of severe bleeding, non-fatal stroke, TIA, SE and vascular death,[39] non-fatal stroke, TIA, SE and vascular death,[39] embolism, stroke, AMI and vascular death,[39] SE and death,[41] and stroke, systemic/coronary ischaemic events, AMI and mortality,[54] and all ischaemic events[54] than anticoagulation alone, the reduction was not significantly different between the ACT and APT vs ACT alone in the two randomised studies.[39,41] Combination therapy conferred a significantly increased risk of the composite end point of stroke, SE and vascular death compared with ACT alone in one randomised study.[43]

Outcome 12: revascularisation procedures

No studies were identified that reported the outcome of revascularisation procedures comparing combined anticoagulant plus APT with ACT alone.

Outcome 13: percentage time in therapeutic international normalised ratio range

Four studies[39,40,42,54] reported in four articles provided outcome data on percentage time in therapeutic INR range (TTR) for ACT in both the intervention (combined anticoagulation plus APT) and comparator (ACT-alone) arms. Of these, three studies[39,40,42] reported randomised comparisons and one study[54] reported non-randomised comparisons. The characteristics of these studies have been reported previously in *Tables 4* and *6*, respectively, and the findings of these studies are reported in *Tables 25* and *26*, respectively.

Lidell *et al*.[40] and the SPAF III study[43] reported TTR for warfarin plus clopidogrel[40] or warfarin plus aspirin[43] and warfarin alone.[40,43] In the study by Lidell *et al*.,[40] TTR was reported to be 100% in both therapy arms,[40] whereas the SPAF III[43] study reported TTR to be 54% in the combined therapy arm and 61% in the warfarin-alone arm.[43] It should be noted that the SPAF III study[43] consisted of a longer follow-up period of a mean of 1.1 years, whereas Lidell *et al*.[40] followed up only 43 patients over a mean follow-up period of 22 days. Furthermore, the SPAF III[43] study used multiple centres utilising testing reagents with multiple sensitivities, whereas Lidell *et al*. [40] report a central assessment laboratory for all samples.

The NASPEAF study[39] reported TTR for acenocoumarol plus triflusal and acenocoumarol alone in high- and intermediate-risk groups. A TTR of 73% was reported in patients receiving combination therapy and 67% in those receiving acenocoumarol alone in the high-risk category. TTR was similar in both therapy arms in the intermediate-risk group (66% in combination therapy arm and 65% in acenocoumarol alone).

TABLE 25 Randomised comparisons reporting TTR of ACT

Author, year	Stroke risk, follow-up, no. of centres[a]	ACT + APT, *n*	TTR [% (SD)] in ACT + APT arm	ACT (alone or ACT + placebo), *n*	TTR [% (SD)] in ACT-alone arm
Pérez-Gómez *et al*., 2004, RCT – NASPEAF[39]	High risk,[b] 2.95 years, NR	Adjusted-dose acenocoumarol (INR 1.4–2.4) + triflusal (600 mg), *n* = 223	73 (22)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 247	67 (22)
	Intermediate risk,[c] 2.6 years, NR	Adjusted-dose acenocoumarol (INR 1.25–2.0) + triflusal (600 mg), *n* = 222	66 (25)	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 232	65 (22)
Lidell *et al*.[40]	Stroke risk NR, 22 days, 1	Adjusted-dose warfarin (INR 2.0–3.0) + clopidogrel (75 mg), *n* = 20	100	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 23	100
SPAF investigators, 1996 RCT – SPAF[43]	High risk,[d] 1.1 years, multiple[e]	Adjusted-dose warfarin (INR 1.2–1.5) + aspirin (325 mg), *n* = 521	54	Adjusted-dose warfarin (INR 2.0–3.0), *n* = 170	61

NR, not reported; SD, standard deviation; NVAF, non-valvular atrial fibrillation; TTR, % time in therapeutic INR range.

a No. of centres involved in conducting INR tests for anticoagulation control.

b Either NVAF with prior embolism or those with mitral stenosis with and without prior embolism.

c NVAF with no embolism at baseline.

d Presence of at least one of the following: impaired left ventricular function manifested by recent (≤100 days) congestive heart disease, or fractional shortening ≤25% by M-mode echocardiography; systolic blood pressure >160 mmHg at study entry; prior ischaemic stroke, TIA or SE (i.e. prior TE); female sex or aged >75 years.

e Multiple clinical laboratories using thromboplastin reagents of varying sensitivities.

TABLE 26 Non-randomised comparisons reporting TTR of the ACT

Author, year	Stroke risk, follow-up, no. of centres[a]	ACT + APT, *n*	TTR % in ACT + APT arm	ACT (alone), *n*	TTR % in ACT-alone arm
Bover *et al.*, 2009[54]	Risk NR. 4.92 years, 2	Adjusted-dose acenocoumarol (INR 1.9–2.5) + triflusal (600 mg), *n* = 155	54.2	Adjusted-dose acenocoumarol (INR 2.0–3.0), *n* = 265	62
		Adjusted-dose acenocoumarol (INR 1.9–2.5) + triflusal (300 mg), *n* = 121	59.1		
		Adjusted-dose acenocoumarol (INR 1.9–2.5) + aspirin (100 mg), *n* = 34	53		

NR, not reported; TTR, % time in therapeutic range.

a No. of centres involved in conducting INR tests for anticoagulation control.

The non-randomised comparison by Bover *et al.*[54] reported a lower TTR in the patients receiving combination acenocoumarol plus triflusal 600 mg (54.2%) and those receiving combination acenocoumarol plus aspirin 100 mg (53%) than in those receiving adjusted-dose acenocoumarol alone (62%). TTR was similar in patients receiving combination acenocoumarol plus triflusal 300 mg to those receiving acenocoumarol alone (59.1% vs 62%, respectively).

The TTR varied markedly between the studies. The study by Lidell *et al.*[40] achieved 100% TTR in both treatment groups, probably as a result of the small sample size and the relatively short follow-up period. In the combined therapy arms of the other two randomised comparisons, TTR was higher in NASPEAF[39] in both the high- and intermediate-risk groups than in the SPAF III[43] study (73% and 66% vs 54%, respectively). TTR was lower in all three combined therapy arms of the non-randomised comparison[54] than in the combined therapy arms in two of the RCTs,[39,40] which may be a reflection of the tighter INR control undertaken in RCTs than in non-RCTs settings but similar to TTR in the SPAF III study.[43] TTR was similar in the anticoagulation-alone arms of NASPEAF[39] (67% and 65% in high- and intermediate-risk patients, respectively), the SPAF III[43] study (61%) and Bover *et al.*[54] (62%).

Summary

Of the four studies[39,40,43,54] that reported percentage TTR, TTR was higher in those receiving combination ACT plus APT in one randomised study,[39] the same (100% TTR) in another randomised study[40], and lower in two other studies[43,54] (one randomised[43] and one non-randomised[54]) than in those receiving ACT alone. INR control, evidenced by TTR, may have impacted on the event rates for each of the outcomes reported.

Summary of results according to interventions and comparator

Vitamin K antagonist plus antiplatelet therapy compared with vitamin K antagonist alone

Warfarin, acenocoumarol and fluindione were the VKAs investigated in the included studies. A summary of their findings according to the intervention and comparator are detailed as follows, and Forrest plots (without summary estimates) are available in *Appendix 8*.

Warfarin plus aspirin compared with warfarin alone

This comparison was investigated in five articles.[42,43,63,68,69] Of these, two studies reported randomised comparisons[42,43] and the remaining three were non-randomised comparisons.[63,68,69] *Table 27* presents the

outcomes of these studies. Warfarin and aspirin dosage differed across the studies, along with significant population heterogeneity.

In both RCTs, AFASAK II[42] and SPAF III,[43] event rates for all categories of stroke were low and similar in patients on combined warfarin [fixed dose[42] or adjusted dose (INR 1.2–1.5)[43]] plus aspirin (300[42] or 325 mg[43]) to those on warfarin [fixed dose[42] or adjusted dose (INR 1.2–1.5)[42,43]] alone, except for ischaemic strokes, for which both studies rates were higher with combination therapy than ACT alone, but not significantly so.

Of the non-randomised comparisons, only Flaker *et al*.[69] reported outcome data for stroke comparing adjusted-dose warfarin (INR 2.0–3.0) plus ≤ 100 mg aspirin with adjusted-dose warfarin (INR 2.0–3.0) alone, indicating a similar rate of strokes across the two arms.

Differences in the rates of TIA and SE outcomes between the study arms was not significantly different in both the AFASAK II[42] and SPAF III studies.[43] No non-randomised study was identified that reported TIA and SE outcome for warfarin plus aspirin compared with warfarin alone.

The rate of the combined end point of stroke and SE was similar across the study arms in the AFASAK II study,[42] whereas the SPAF III[43] study reported higher rates in patients on combined warfarin plus aspirin than in those with adjusted-dose warfarin (INR 2.0–3.0) alone. The non-randomised comparison by Flaker *et al*.[69] demonstrated similar rates across the study arms. A subgroup of patients from this cohort with a history of previous embolism was analysed by Akins *et al*.,[68] demonstrating a higher proportion of patients in the combined therapy arm suffering the end point of stroke or SE than in those on warfarin alone.

The SPAF III[43] and AFASAK II[42] RCTs did not demonstrate a significant difference in the event rates of AMI between combination therapy and warfarin alone. Flaker *et al*.,[69] in their non-randomised comparison also demonstrated similar events of AMI in patients on combined therapy compared with those on warfarin alone.

Similar rates of vascular mortality were observed across the study arms in the two RCTs.[42,43] No non-randomised comparisons were identified that reported vascular mortality comparing combined warfarin plus aspirin with warfarin alone.

The AFASAK II[42] and SPAF III[43] studies demonstrated no significant difference in the rates of all-cause mortality in the combined therapy arms compared with adjusted-dose warfarin (INR 2.0–3.0) alone. Flaker *et al*.[69] reported a similar proportion of all-cause mortality across arms in a non-randomised comparison.

Similar rates of haemorrhage (intracranial, major and minor) were reported in the combined therapy group compared with warfarin alone in both the AFASAK II[42] and SPAF III[43] studies. Of the non-randomised comparisons, Hansen *et al*.[63] reported a smaller proportion of patients suffering a haemorrhagic event in patients on combined therapy than in those on warfarin alone, in a large non-randomised cohort of patients with AF ($n = 118{,}606$), followed up over a period of 3.3 years. The study by Flaker *et al*.,[69] however, demonstrated a higher proportion of patients experiencing haemorrhage in the combined therapy group than in those on warfarin alone over a period of 16.5 months.

Significantly higher rates of the composite end point of stroke, SE and vascular death were reported in patients on combined warfarin plus aspirin than in those on warfarin alone in the SPAF III study.[43] No other study reported outcomes for this comparison.

The SPAF III[43] RCT reported TTRs that were within the therapeutic range (in this case between INR 1.5–2.5) for patients on combined therapy for 54% of the time and those on warfarin alone were reported to be within therapeutic range (INR 2.0–3.0) for 61% of the time.

Of the studies that reported randomised comparisons, the AFASAK II study[42] was prematurely terminated when results of the SPAF-III trial[42] were published, demonstrating the superiority of adjusted-dose warfarin (INR 2.0–3.0) alone, over the combination of adjusted-dose warfarin (INR 1.2–2.5) and aspirin 325 mg, in preventing stroke or SE.[42] Both of these comparisons used different open-label warfarin regimes in the combination and comparator arm, and different doses of aspirin (300 mg AFASAK II[42] and 325 mg SPAF III[43]), and had varying lengths of follow-up (mean 3.5 years in the AFASAK II[42] study and mean 1.1 years in the SPAF III[43] study). The SPAF III[43] study did not consider diabetes mellitus a stroke risk factor, which could have introduced patients at lower risk of stroke into the study, whereas the AFASAK II[42] study did not specify stroke risk. Of the non-randomised studies, aspirin was administered at the physician's discretion.[63,69] One study was conducted on hospitalised patients in whom the dosage of warfarin and aspirin was not reported.[63] These factors make it potentially difficult to infer a clear effect of combined therapy on vascular events in a high-risk AF population.

Warfarin plus clopidogrel compared with warfarin alone

This comparison was investigated in two studies, of which one was a randomised comparison[40] (the other reported a non-randomised comparison[63]). *Table 27* presents the outcomes of these studies. Of note is the dearth of studies conducted on a group of patients with AF at a specified high risk of stroke randomised to combined therapy of adjusted-dose warfarin (INR of 2.0–3.0) plus clopidogrel and adjusted-dose warfarin (INR 2.0–3.0) alone.

Data were available only for rates of haemorrhage in these two studies. Lidell *et al*.[40] reported very low event rates for minor haemorrhage in a randomised comparison of a small, predominantly male, sample size ($n = 43$), followed up over a very short period of time (22 days). Furthermore, Hansen *et al*.[63] reported a higher proportion of patients suffering from haemorrhage in the warfarin group than in the combined therapy group in a large sample size ($n = 118,606$) of hospitalised patients followed up over a period of 3.3 years. Clopidogrel was administered according to physician's discretion in this study. Furthermore, the dosage of both warfarin or clopidogrel was unknown in this study.[63] Therefore, from the available evidence, it is difficult to determine the effect of combined therapy on vascular events.

Warfarin plus aspirin plus clopidogrel (triple therapy) compared with warfarin alone

One non-randomised study[63] investigated this comparison.[63]

Data were available only for rates of haemorrhage for this comparison. Hansen *et al*.[63] reported a higher proportion of patients suffering from haemorrhage in the warfarin-only group than in the triple therapy group. Although the study was conducted on a large sample size ($n = 118,606$) over a mean of 3.3 years of follow-up, the dosage of warfarin, aspirin or clopidogrel was not reported. Furthermore, APT was administered at physician's discretion. The evidence is, therefore, insufficient to determine the benefit of combined therapy over warfarin alone for vascular events.

Fluindione plus aspirin compared with fluindione alone

This comparison was investigated in one randomised study[41] comparing fluindione (INR 2.0–2.6) plus aspirin (100 mg) with fluindione (INR 2.0–2.6) plus placebo in high-risk patients with AF over a mean follow-up period of 0.84 years. Non-randomised evidence was not identified for this comparison.

The study[41] reported very low event rates of SE, vascular death, all-cause mortality, and the composite end point of non-fatal SE and vascular death, with non-significant differences between combined therapy and fluindione plus placebo. However, a significantly higher rate of haemorrhage was observed in patients on combination therapy than in those on fluindione plus placebo. The study was conducted on a small sample size ($n = 157$) over a mean follow-up period of 0.84 years on a high-risk AF population, 85% of whom were anticoagulant experienced at entry. Of note is the low event rate and premature termination of the trial because of a low enrolment rate. All of these factors render it difficult to meaningfully evaluate the benefit of combination therapy over anticoagulant alone for this combination.

Acenocoumarol plus aspirin compared with acenocoumarol alone

This comparison was investigated in one non-randomised comparison by Bover *et al.*,[54] comparing adjusted-dose acenocoumarol targeting an INR range of 1.9–2.5 plus aspirin 100 mg with adjusted-dose acenocoumarol (INR 2.0–3.0) alone. The study[54] also compared the combination of acenocoumarol plus different regimes of triflusal (300 and 600 mg) with acenocoumarol alone. These comparisons have been reported in previous sections. Many of the patients in the study had been participants in the NASPEAF RCT;[39] however, it was difficult to identify which patients these were, what – if any –subsequent treatment they received and, thus, their influence on the findings of this non-randomised comparison.[54]

The study[54] reported a very small number of outcome events, with fewer events of strokes (total), SE and AMI in the combined therapy group than in the acenocoumarol-alone group. The study[54] also reported the composite end points of ischaemic events, stroke, AMI and mortality with no significant differences in events in patients on combined therapy compared with those on acenocoumarol alone. However, patients on combination therapy demonstrated more non-cardiac and sudden deaths, along with a greater prevalence of severe, fatal, and non-GI bleeding than those on acenocoumarol alone.

Of note is, the considerably greater prevalence of stroke risk factors in the patients on acenocoumarol plus aspirin (embolism or age >75 years, males, HF, diabetes mellitus, dyslipidaemia, coronary disease, smokers) than in those on acenocoumarol alone.[54] There were very few patients in the combined therapy group ($n = 34$) compared with those on acenocoumarol alone ($n = 265$). Therefore, it is difficult to conclude the benefit of combined therapy over acenocoumarol alone.

Acenocoumarol plus triflusal compared with acenocoumarol alone

This comparison was investigated in two studies: one reporting a randomised comparison[39]and one a non-randomised comparison.[54] No study was identified with a clearly specified group of patients with AF, at a high-risk of stroke, randomised to combination therapy of adjusted-dose acenocoumarol targeting an INR of 2.0–3.0 plus triflusal and adjusted-dose acenocoumarol (INR 2.0–3.0) alone.

Acenocoumarol and triflusal dosage differed between the studies. The NASPEAF study[39] compared adjusted-dose acenocoumarol in different regimes (INR 1.4–2.4 and INR 1.25–2.0) plus triflusal 600 mg, with adjusted-dose acenocoumarol (INR 2.0–3.0) alone in patients at a high risk and intermediate risk of stroke. Bover *et al.*[54] compared adjusted-dose acenocoumarol (INR 1.9–2.5) combined with different regimes of triflusal (600 mg, 300 mg) with adjusted-dose acenocoumarol (INR 2.0–3.0) alone, wherein most patients consisted of previously randomised patients in the NASPEAF RCT.[39] As mentioned previously it was difficult to identify the specific distribution of these patients.[54] It is also important to note that patients on combined therapy had more stroke risk factors than patients on acenocoumarol alone (combination with triflusal 600 mg; greater percentage of patients with previous embolism and dyslipidaemia; combination therapy with triflusal 300 mg consisted of more patients with previous embolism or age >75 years, diabetes mellitus, dyslipidaemia).

The NASPEAF RCT[39] reported no difference in rates of non-fatal stroke between combination ACT plus APT and ACT alone in either a high- or intermediate-risk population.[39] Bover *et al.*[54] reported a higher proportion of patients on acenocoumarol alone suffering a stroke than in those on combination therapy with acenocoumarol plus triflusal 600 mg, whereas a similar number of events were reported in patients on combined acenocoumarol and triflusal 300 mg than in those receiving acenocoumarol alone (see *Table 27*).

Similar rates of TIA were observed in both treatment arms in the high- and intermediate-risk population in the NASPEAF RCT.[39] No non-randomised evidence was identified reporting TIA for this comparison.

Very few events of non-fatal SE were observed in the NASPEAF study.[39] The non-randomised comparison study by Bover *et al.*[54] demonstrated fewer events of SE in patients on combined therapy (with either triflusal 600 mg or 300 mg) than in those on acenocoumarol alone.

Rates of the combined end point of stroke and SE were similar across the arms in both the high-risk group as well as the intermediate-risk group in the NASPEAF study.[39] Non-randomised comparisons were not identified for this end point.

No AMI events were reported in the NASPEAF study.[39] However, Bover *et al*.[54] demonstrated slightly fewer AMI events in patients on combined therapy (with either triflusal 600 mg or 300 mg) than in those on acenocoumarol alone.[54]

The NASPEAF study[39] demonstrated significantly lower rates of vascular mortality in patients on combined acenocoumarol plus triflusal 600 mg than in those on acenocoumarol alone in both the high- and intermediate-risk groups.

A non-significant lower rate of all-cause mortality was reported in the high-risk group in the NASPEAF study[39] for the combination therapy. This difference was more pronounced in intermediate-risk patients and reached statistical significance. A lower rate of all-cause mortality was reported in patients on combined therapy than in those on acenocoumarol alone in the intermediate-risk group.[39] Furthermore, Bover *et al*.,[54] in their non-randomised comparison, reported a higher proportion of non-cardiac deaths in patients on combined therapy (acenocoumarol plus either triflusal 600 mg or triflusal 300 mg) than in those on acenocoumarol alone.

No significant differences in the rates of intracranial, severe, non-severe or gastrointestinal (GI) haemorrhage were reported in the randomised NASPEAF study[39] comparing the combination of acenocoumarol plus triflusal with acenocoumarol alone in high- and intermediate-risk patients.[39] Bover *et al*.[54] reported a smaller proportion of patients suffering a severe, fatal or a non-GI haemorrhage in the combined therapy group(s) (acenocoumarol plus either triflusal 600 mg or triflusal 300 mg) than in the acenocoumarol-alone group. However, more patients in the combination therapy group(s) demonstrated GI bleeding than those on acenocoumarol alone.

The rate of the combined end points of non-fatal stroke, TIA, SE and vascular death was significantly lower in patients on combined acenocoumarol plus additional triflusal 600 mg than in those on acenocoumarol alone in both high- and intermediate-risk groups.[39] A similar trend was observed for the combined end point of severe bleeding, non-fatal stroke, TIA, SE and vascular death in the intermediate-risk group in the NASPEAF study.[39] Furthermore, Bover *et al*.[54] reported fewer events of composite end points (ischaemic events, and stroke, systemic events, AMI and mortality) in the combined therapy group(s) than in the acenocoumarol-alone group.

The NASPEAF study[39] reported slightly better TTR of acenocoumarol in the combination therapy arm than in the acenocoumarol-alone arm in the high-risk group. However, in a non-randomised comparison, Bover *et al*.[54] reported slightly better TTR in patients on acenocoumarol alone than in those on combination therapy of acenocoumarol plus either triflusal 300 mg or 600 mg.

Overall, there seem to be fewer negative events in the combined therapy arms, with statistically significant differences in the mortality rates and composite end points, than in the acenocoumarol-alone arms in either the high- or the intermediate-risk groups in the randomised NASPEAF study.[39] However, there seems to be no statistically significant difference in rate of haemorrhage between the two arms in either risk group.[39] A similar trend was demonstrated in the non-randomised comparison by Bover *et al*.,[54] with fewer patients suffering stroke, SE, bleeding and composite end points in the combined therapy group than in the acenocoumarol-alone group.

TABLE 27 Outcomes reported according to the intervention and comparator

Name of study	Population, design Study design, stroke risk, follow-up	Intervention: ACT + APT Dose of ACT, dose of APT (*n*)	Comparator: ACT only Dose (*n*)	Outcomes: event % in ACT + APT vs event % in ACT alone, RR (95% CI) Stroke	TIA	SE
Warfarin + aspirin vs warfarin alone						
Gullov *et al.*, 1998 (RCT – AFASAK II[42])	Rand, risk NR, 3.5 years	Fixed dose 1.25 mg, 300 mg (171)	Adjusted dose INR 2.0–3.0, (170)	All: 6.4 vs 5.9, *1.09 (0.48 to 2.51)* Non-infarct: 1.8 vs 1.8, *0.99 (0.20 to 4.86)* Minor: 2.3 vs 0, *8.95 (0.49 to 164.92)* Disabling: 2.3 vs 1.8, *1.33 (0.30 to 5.83)* Fatal: 0 vs 0 *to not estimable* Haemorrhagic: 0 vs 0.6, *0.33 (0.01 to 8.08)* Ischaemic: 4.7 vs 1.8, *2.65 (0.72 to 9.82)* Non-disabling: 1.8 vs 2.4, *0.75 (0.17 to 3.28)*	1.2 vs 0.6, *1.99 (0.18 to 21.72)*	All: 0.6 vs 1.2, 0.50 (0.05 to 5.43) Fatal: 0.6 vs 0, *2.98 (0.12 to 72.70)*
		–	Fixed dose 1.25 mg, (167)	All: 6.4 vs 7.8, *0.83 (0.38 to 1.79)* Non-infarct: 1.8 vs 3.6, *0.49 (0.12 to 1.92)* Minor: 2.3 vs 1.8, *1.30 (0.30 to 5.73)* Disabling: 2.3 vs 1.2, *1.95 (0.36 to 10.52)* Fatal: 0 vs 1.2 *to 0.20 (0.01 to 4.04)* Haemorrhagic: 0 vs 0, *not estimable* Ischaemic: 4.7 vs 2.9, *1.56 (0.52 to 4.68)* Non-disabling: 1.8 vs 2.4, *0.73 (0.17 to 3.22)*	1.2 vs 2.4, *0.49 (0.09 to 2.63)*	All: 0.6 vs 0.6, *0.98 (0.06 to 15.49)* Fatal: 0.6 vs 0.6, *0.98 (0.06 to 15.49)*

Stroke + SE	AMI	Vascular mortality	All-cause mortality	Bleeding (any)	TTR	Composite events
7.0 vs 7.1, *0.99 (0.46 to 2.15)*	0 vs 2.4, *0.11 (0.01 to 2.04)*	1.8 vs 2.9, *0.60 (0.14 to 2.46)*	Total: 5.3 vs 3.6, *1.46 (0.53 to 4.03)* Non-vascular: 0.6 vs 0, *2.93 (0.12 to 71.42)* Unknown cause: 1.2 vs 1.2, *0.98 (0.14 to 6.85)*	ICH: 0 vs 1.2, 0.19 (0.01 to 4.11) Major: 0.6 vs 2.4, 0.25 *(0.03 to 2.20)* Minor: 16.4 vs 24.7, 0.66 *(0.43 to 1.02)*	N/A	NR
7.0 vs 8.4, *0.84 (0.40 to 1.76)*	0 vs 3.6, *0.08 (0.00 to 1.32)*	1.8 vs 1.2, *1.46 (0.25 to 8.66)*	Total: 5.3 vs 10.0, *0.53 (0.24 to 1.15)* Non-vascular: 0.6 vs 1.2, *0.50 (0.05 to 5.43)* Unknown cause: 1.2 vs 1.8, *0.66 (0.11 to 3.92)*	ICH: 0 vs 0.6, *0.33 (0.13 to 7.94)* Major: 0.6 vs.1.8, *0.33 (0.03 to 3.09)* Minor: 16.4 vs.12.6, *1.30 (0.77 to 2.19)*	N/A	NR

continued

TABLE 27 Outcomes reported according to the intervention and comparator (*continued*)

Name of study	Population, design Study design, stroke risk, follow-up	Intervention: ACT + APT Dose of ACT, dose of APT (*n*)	Comparator: ACT only Dose (*n*)	Outcomes: event % in ACT + APT vs event % in ACT alone, RR (95% CI) Stroke	TIA	SE
SPAF investigators, 1996 (RCT – SPAF III)[43]	Randomised, high risk,[a] NR, 3.5 years	Adjusted dose INR 1.2–1.5, 325 mg (521)	Adjusted dose INR 2.0–3.0 (523)	Disabling: 5.9 vs 1.9, *2.83 (1.44 to 5.57)* Ischaemic: 8.3 vs 2.1, *3.92 (2.05 to 7.52)* Ischaemic (fatal): 0.9 vs 0.2, *5.02 (0.59 to 42.81)*	4.4 vs 2.9, 1.54 (0.81 to 2.92)	0.2 vs 0, 3.01 (0.12 to 73.75)
Hansen *et al.*, 2010[63]	Non-randomised, risk NR, 3.3 years	NR, NR (18,345)	NR (50,919)	NR	NR	NR
Flaker *et al.*, 2006[69]	Non-randomised, high risk,[b] 16.5 months	Adjusted dose INR 2.0–3.0, ≤100 mg (481)	Adjusted dose INR 2.0–3.0 (3172)	All: 2.3 vs 2.1	NR	NR
Akins *et al.*, 2007[67]	Non-randomised, high risk[b], 16.5 months	Adjusted dose INR 2.0–3.0, ≤100 mg (156)	Adjusted dose INR 2.0–3.0 (567)	NR	NR	NR
Warfarin + clopidogrel vs warfarin alone						
Lidell *et al.*, 2003 [40]	Randomised, risk NR, 22 days	Adjusted dose INR 2.0–3.0, 75 mg (20)	Adjusted dose INR 2.0–3.0 (23)	NR		NR
Hansen *et al.*, 2010 [63]	Non-randomised, risk NR, 3.3 years	NR, NR (1430)	NR (50,919)	NR		NR
Warfarin + aspirin + clopidogrel vs warfarin alone						
Hansen *et al.*, 2010[63]	Non-randomised, risk NR, 3.3 years	NR, NR (1261)	NR (50,919)	NR		NR

Stroke + SE	AMI	Vascular mortality	All-cause mortality	Bleeding (any)	TTR	Composite events
8.4 vs 2.1, 4.02 (2.10 to 7.69)	1.9 vs 1.0, 2.01 (0.69 to 5.83)	5.2 vs 5.2, 1.00 (0.60 to 1.69)	Total: 8.1 vs 6.7, 1.20 (0.78 to 1.86) Non-vascular: 2.3 vs 1.5, 1.51 (0.62 to 3.65) Indeterminant: 0.6 vs 0, 7.00 (0.36 to 135.18)	ICH: 0.9 vs 0.6, 1.67 (0.40 to 6.96) Major: 2.5 vs 2.3, 1.08 (0.50 to 2.36) Minor: 1.2 vs 0.8, 1.5 (0.43 to 5.30)	54 vs 61	Stroke, SE, vascular death: 12.7 vs 7.1, 1.79 (1.22 to 2.63)
NR	NR	NR	NR	All: 6.6 vs 7.2	NR	
2.3 vs 2.2	0.8 vs 1.5	NR	3.5 vs 3.5	Major: 5.2 vs 3.2 Major/minor: 52.2 vs 37.8	NR	
6.9 vs 4.1	NR	NR	NR	NR	NR	
NR	NR	NR	NR	Minor: 0 vs 21.8, 0.10 (0.01 to 1.77)	100 vs 100	
NR	NR	NR	NR	All: 4.8 vs 7.2	NR	
NR	NR	NR	NR	All: 5.1 vs 7.2	NR	

continued

TABLE 27 Outcomes reported according to the intervention and comparator (*continued*)

Name of study	Population, design Study design, stroke risk, follow-up	Intervention: ACT + APT Dose of ACT, dose of APT (*n*)	Comparator: ACT only Dose (*n*)	Outcomes: event % in ACT + APT vs event % in ACT alone, RR (95% CI) Stroke	TIA	SE
Acenocoumarol + aspirin vs acenocoumarol alone						
Bover *et al.*, 2009[54]	Non-randomised, risk NR, 4.92 years	Adjusted dose INR 1.9–2.5, 100 mg (34)	Adjusted dose INR 2.0–3.0 (265)	All: 2.9 vs 5.7 Haemorrhagic: 2.9 vs 1.9 Lethal: 2.9 vs 1.5	NR	0 vs 2.6
Acenocoumarol + triflusal vs acenocoumarol alone						
Pérez-Gómez *et al.*, 2004, (RCT – NASPEAF[39])	Randomised, high risk,[c] 2.95 years	Adjusted dose INR 1.4–2.4, 600 mg (223)	Adjusted dose INR 2.0–3.0 (247)	Non-fatal: 2.7 vs 2.4, *1.11 (0.36 to 3.38)*	0.9 vs 1.2, *0.74 (0.12 to 4.38)*	Non-fatal: 0 vs 1.2, *0.16 (0.01 to 3.05)*
	Randomised, intermediate risk,[e] 2.6 years	Adjusted dose INR 1.25–2.0, 600 mg (222)	Adjusted dose INR 2.0–3.0 (232)	Non-fatal: 1.4 vs 1.3, *1.05 (0.21 to 5.12)*	0 vs 0, *not estimable*	Non-fatal: 0 vs 0.4, *0.35 (0.01 to 8.50)*
Bover *et al.*, 2009[54]	Non-randomised, risk NR, 4.92 years	Adjusted dose INR 1.9–2.5, 600 mg (155)	Adjusted dose INR 2.0–3.0 (265)	All: 3.2 vs 5.7 Haemorrhagic: 0.6 vs 1.9 Lethal: 1.3 vs 1.5	NR	0 vs 2.6
		Adjusted dose INR 1.9–2.5, 300 mg (120)	Adjusted dose INR 2.0–3.0 (265)	All: 6.7 vs 5.7 Haemorrhagic: 0 vs 1.9 Lethal: 2.5 vs 1.5	NR	1.7 vs 2.6

Stroke + SE	AMI	Vascular mortality	All-cause mortality	Bleeding (any)	TTR	Composite events
NR	0 vs 1.9	NR	Non-cardiac: 2.9 vs 1.1 Sudden: 2.9 vs 1.1	Severe: 20.6 vs 12.1 Fatal: 5.9 vs 2.6 GI: 0 vs 2.3 Non-GI: 20.6 vs 9.8	53 vs 62	Ischaemic events (all): 0 vs 8.3 Stroke, systemic/ coronary ischaemic events, AMI and mortality: 8.8 vs 13.9
Stroke[d]/any embolism: 5.4 vs 8.1, *0.66 (0.33 to 1.33)* Stroke[d]/fatal embolism: 1.8 vs 3.2, *0.55 (0.17 to 1.81)*	0 vs 0, *not estimable*	2.7 vs 6.9, *0.39 (0.16 to 0.97)*	Total: 5.4 vs 9.3, 0.58 *(0.29 to 1.13)* Non-vascular: 2.7 vs 2.4, *1.11 (0.36 to 3.38)*	ICH: 0.9 vs 2.0, *0.44 (0.09 to 2.26)* Severe: 5.4 vs 5.3, *1.02 (0.47 to 2.19)* Severe – other: 0.9 vs 2.0, *0.44 (0.09 to 2.26)* Non-severe: 8.9 vs 7.3, *1.23 (0.67 to 2.27)* GI: 3.6 vs 1.2, *2.95 (0.79 to 10.99)*	73 vs 67	Severe bleeding, non-fatal stroke, TIA, SE and vascular death: 9.9 vs 13.8, *0.72 (0.43 to 1.19)* Embolism, stroke, AMI and vascular death: 5.8 vs.10.1, *0.58 (0.30 to 1.10)* Non-fatal stroke, TIA, SE, and vascular death: 6.3 vs 11.7, *0.53 (0.29 to 0.99)*
Stroke[d]/any embolism: 1.4 vs 3.0, *0.45 (0.12 to 1.71)* Stroke[d]/fatal embolism: 0 vs 1.3, *0.15 (0.01 to 2.87)*	0 vs 0, *not estimable*	0.9 vs 4.7, *0.19 (0.04 to 0.85)*	Total: 2.7 vs 8.6, *0.31 (0.13 to 0.77)* Non-vascular: 1.8 vs 3.9, *0.46 (0.15 to 1.49)*	ICH: 0.5 vs 1.7, *0.48 (0.05 to 4.21)* Severe:[d] 2.3 vs 4.3, *0.52 (0.18 to 1.50)* Severe – other: 0.5 vs 2.2, *0.21 (0.02 to 1.77)* Non-severe: 7.2 vs 6.5, *1.11 (0.56 to 2.20)* GI: 1.4 vs 0.43, *3.13 (0.33 to 29.91)*	66 vs 65	Severe bleeding, non-fatal stroke, TIA, SE and vascular death: 3.6 vs 9.1 *to 0.40 (0.18 to 0.88)* Embolism, stroke, AMI and vascular death: 1.8 vs 3.4, *0.52 (0.16 to 1.71)* Non-fatal stroke, TIA, SE, and vascular death: 2.3 vs 16.5, *0.35 (0.13 to 0.94)*
NR	0 vs 1.9	NR	Non-cardiac: 3.9 vs 1.1 Sudden: 2.6 vs 1.1	Severe: 6.5 vs 12.1 Fatal:0 vs 2.6 GI: 5.2 vs 2.3 Non-GI: 1.3 vs 9.8	54.2 vs 62	Ischaemic events (all): 2.6 vs 8.3 Stroke, systemic/ coronary ischaemic events, AMI and mortality: 5.8 vs 13.9
NR	0.8 vs 1.9	NR	Non-cardiac: 2.5 vs 1.1 Sudden: 0 vs 1.1	Severe: 5.0 vs 12.1 Fatal: 0.8 vs 2.6 GI: 4.2 vs 2.3 Non-GI: 0.8 vs 9.8	59.1 vs 62	Ischaemic events (all): 9.2 vs 8.3 Stroke, systemic/ coronary ischaemic events, AMI and mortality: 10.0 vs 13.9

continued

TABLE 27 Outcomes reported according to the intervention and comparator (*continued*)

Name of study	Population, design Study design, stroke risk, follow-up	Intervention: ACT + APT Dose of ACT, dose of APT (*n*)	Comparator: ACT only Dose (*n*)	Outcomes: event % in ACT + APT vs event % in ACT alone, RR (95% CI) Stroke	TIA	SE
Dabigatran + aspirin vs dabigatran alone						
Ezekowitz *et al.*, 2007 (RCT – PETRO)[73]	Non-randomised, ≥ stroke risk criteria,[f] 12 weeks	300 mg,[d] 81 mg (34)	300 mg[d] (105)	NR	NR	0 vs 0
		300 mg,[d] 325 mg (30)		NR	NR	0 vs 0
		150 mg,[d] 81 mg (36)	150 mg[d] (100)	NR	NR	0 vs 0
		150 mg,[d] 325 mg (33)		NR	NR	0 vs 0
		50 mg,[d] 81 mg (21)	50 mg[d] (59)	NR	NR	4.8 vs 1.7
		50 mg,[d] 325 mg (27)		NR	NR	0 vs 1.7
Fluindione + aspirin vs fluindione alone						
Lechat *et al.*, 2001 (RCT – FFAACS[41])	Randomised, high risk,[g] 0.82 years	Adjusted dose INR 2.0–2.6, 100 mg (76)	Adjusted dose INR 2.0–2.6 (81)	NR	NR	TE: 2.6 vs 1.2, *2.13 (0.20 to 23.03)*

Stroke + SE	AMI	Vascular mortality	All-cause mortality	Bleeding (any)	TTR	Composite events
NR	NR	NR	NR	Major: 2.9 vs 0 Clinical relevant + major: 14.7 vs 5.7 All: 32.4 vs 13.3	N/A	
NR	NR	NR	NR	Major: 10.0 vs 0 Clinical relevant + major: 20.0 vs 5.7 All: 46.7 vs 13.3	N/A	
NR	NR	NR	NR	Major: 0 vs 0 clinical relevant + major: 5.6 vs 9.0 All: 22.2 vs 15.0	N/A	
NR	NR	NR	NR	Major: 0 vs 0 clinical relevant + major: 6.1 vs 9.0 All: 21.2 vs 15.0	N/A	
NR	NR	NR	NR	Major: 0 vs 0 clinical relevant + major: 4.8 vs 0 All: 9.5 vs 3.4	N/A	
NR	NR	NR	NR	Major: 0 vs 0 clinical relevant + major: 3.7 vs 0 All: 11.1 vs 3.4	N/A	
NR	NR	3.9 vs 2.5, *1.60 (0.27 to 9.31)*	3.9 vs 3.7, *1.07 (0.22 to 5.12)*	Severe: 3.9 vs 1.2, *3.19 (0.34 to 30.07)* Non-severe: 13.2 vs 1.2, *10.66 (1.39 to 81.28)* All: 17.1 vs 2.5, *6.93 (1.62 to 29.69)*	NR	SE, death: 6.6 vs 2.5, 2.66 (0.53 to 13.33)

continued

TABLE 27 Outcomes reported according to the intervention and comparator (*continued*)

Name of study	Population, design Study design, stroke risk, follow-up	Intervention: ACT + APT Dose of ACT, dose of APT (*n*)	Comparator: ACT only Dose (*n*)	Outcomes: event % in ACT + APT vs event % in ACT alone, RR (95% CI) Stroke	TIA	SE
Ximelagatran + aspirin vs ximelagatran alone						
Flaker *et al.*, 2006[69]	Non-randomised, high risk,[b] 16.5 months	36 mg,[d] 100 mg (531)	36 mg[d] (3120)	All: 2.1 vs 1.6	NR	NR
Akins *et al.*, 2007[67]	Non-randomised, high risk,[h] 16.5 months	36 mg,[d] 100 mg (157)	36 mg[d] (629)	NR	NR	NR

CNS, central nervous system; N/A, not available; NVAF, non-valvular atrial fibrillation; NR, not reported.

a Presence of at least one of the following: impaired LV function manifested by recent (≤100 days) congestive heart disease, or fractional shortening ≤25% by M-mode echocardiography; systolic blood pressure >160 mmHg at study entry; prior ischaemic stroke, TIA or SE (i.e. prior TE); female sex or aged >75 years.

b Previous stroke/TIA/SE, hypertension, left ventricular dysfunction (ejection fraction <40% or symptomatic systolic or diastolic HF), aged ≥75 years or aged ≥65 years with known coronary disease/diabetes mellitus.

c Either NVAF with prior embolism or those with mitral stenosis with and without prior embolism.

d ACT was administered twice daily.

e NVAF with no embolism at baseline.

f CAD + at least one of the following: hypertension requiring medical treatment, diabetes mellitus (type 1 or 2), symptomatic HF or left ventricular dysfunction (ejection fraction <40%), previous stroke or TIA, aged >75 years.

g Either one: history of TE (TIA, non-disabling ischaemic stroke or peripheral embolism) or aged >65 years and at least one of the following: history of hypertension (systolic arterial pressure of >160 mmHg or diastolic arterial pressure of >90 mmHg); recent episode (<3 months previously) of congestive HF or alteration in left ventricular function (echocardiographic left ventricular shortening fraction of <25% or LVEF <40% within 3 months before study inclusion).

h All patients with history of previous embolism.

Stroke + SE	AMI	Vascular mortality	All-cause mortality	Bleeding (any)	TTR	Composite events
2.3 vs 1.9	1.9 vs 1.3	NR	0.6 vs 3.0	Major: 0.4 vs 2.5 Major/minor: 38.0 vs 32.5	N/A	
7.0 vs 3.5	NR	NR	NR	NR	N/A	

Other anticoagulants

Dabigatran and ximelagatran do not belong to the VKA class of anticoagulant and, therefore, have been dealt with separately in the sections below.

Dabigatran plus aspirin compared with dabigatran alone

This comparison was investigated in the PETRO[73] study comparing different regimes of dabigatran (50/150/300 mg twice daily) plus aspirin 81 mg or 325 mg doses with adjusted-dose dabigatran (50/150/300 mg twice daily) alone.

This PETRO study[73] reported none or very small number of systemic embolic events in each therapy group. A higher proportion of patients on combined dabigatran (300/150/50 mg twice daily) plus aspirin (81 or 325 mg) experienced a haemorrhagic event than in those on dabigatran (300/150/50 mg twice daily) alone.

The PETRO study[73] was conducted on a sample of 502 antithrombotic-experienced patients with AF (82% males) at a high risk of stroke over a follow-up period of 12 weeks.[73] However, after entry of about half of the patients, the requirement for patients to have a history of CAD was removed to facilitate inclusion, which could have allowed inclusion of lower-risk patients as well. The numerical distribution of patients in each group (dabigatran and dabigatran plus aspirin) was uneven, and it was not clear if aspirin was administered at random or conditionally. Therefore, the benefit or harm of combined therapy over anticoagulant alone is not clear for this comparison.

Ximelagatran plus aspirin compared with ximelagatran alone

This comparison was investigated in the pooled analyses of the SPORTIF trials (SPORTIF III[64] and SPORTIF V[65]) by Flaker *et al*.,[69] and Akins *et al*.,[67] comparing ximelagatran (36 mg twice daily) plus aspirin (100 mg), with ximelagatran (36 mg twice daily) alone. The study by Flaker *et al*.[69] demonstrated that a higher proportion of patients on combined ximelagatran plus aspirin suffered a stroke, AMI, haemorrhage, or combined end point of stroke and SE than those on ximelagatran alone. Akins *et al*.[67] conducted an analysis on a high-risk subgroup (those with history of embolism) for the same cohort, and demonstrated a similar trend for the combined end point of stroke and SE (*Table 27*). Furthermore, Flaker *et al*.[69] demonstrated fewer major bleeding events and lower all-cause mortality in the combination arm than in those on ximelagatran alone. The SPORTIF trials[64,65] were conducted on patients with AF with at least one risk factor for stroke over a mean follow-up of 16.5 months. Aspirin was indicated for patients with CAD, and there were significant baseline differences between patients administered combined therapy and those on anticoagulant alone.[69] There was no randomised evidence identified for this comparison. Therefore, the benefit of combination therapy over ximelagatran alone is difficult to evaluate from the available evidence.

Chapter 4 Discussion

Statement of principal findings

The purpose of this review was to assess the clinical effectiveness of adding APT to ACT compared with ACT alone in reducing vascular events in patients with AF at a high risk of TEs resulting from atrial fibrillation.

Clinical effectiveness

A total of five studies[39–43] that reported randomised comparisons, and 18[50–65,72,73] that reported non-randomised comparisons, were included in this assessment.

Overall, there were few stroke events reported with conflicting evidence regarding the benefit of ACT plus APT over ACT alone in the reduction of all stroke events, with two studies (one randomised[42] and one non-randomised[69]) reporting no differences, whereas another non-randomised study[54] reports equivocal data, demonstrating fewer strokes with two combination regimes of ACT plus APT over ACT alone.[54]

Studies that differentiated between types of strokes did not report significant differences in the rates between patients on ACT plus APT and those on ACT alone. Two randomised studies[42,43] and one non-randomised study[54] found no significant reduction in the risk of fatal stroke with ACT plus APT over ACT alone. Furthermore, combination therapy did not decrease the risk of non-fatal stroke compared with anticoagulation alone in another randomised study.[39] Of the few events reported in one randomised[42] and one non-randomised[54] study, there was no evidence of an increased risk of haemorrhagic stroke with combination ACT plus APT over ACT alone. There is conflicting evidence regarding the benefit of combination therapy in the reduction of ischaemic stroke, with one randomised study[42] demonstrating no significant difference, whereas another randomised study suggests a significantly increased risk of ischaemic stroke with combination therapy.[43] There is also conflicting evidence regarding the benefit of combination ACT plus APT compared with ACT alone in the reduction of disabling stroke, with one randomised study[42] demonstrating no significant difference, whereas another randomised study[43] suggests a significantly increased risk of disabling stroke with combination therapy. However, given the methodological heterogeneity and study quality issues, it is difficult to comment on a clear benefit of one therapeutic regime over another.

No significant benefit of combination therapy over anticoagulation alone was observed to reduce the risk of TIAs.[39,42,43]

The majority of included studies do not provide significant evidence of any benefit for combination therapy over ACT alone in the reduction of the combined end point of stroke and SE from two randomised[39,42] and two non-randomised[67,69] studies, apart from one RCT[43] that suggests a significant increased risk of the combined end point of stroke and SE with the combination of ACT and APT compared with ACT alone.

There is also no evidence that combination ACT plus APT is associated with a significant reduction in systemic embolic events compared with ACT alone in the included studies.

There is no clear evidence of a significant benefit of combination therapy in the reduction of AMI despite numerically lower rates of the event with combined ACT plus APT than with ACT alone.[42,43,54,69]

The available evidence does not indicate a clear benefit of combination therapy in reducing the risk of vascular death compared with ACT alone.[39,41–43] In a similar way, six studies[39,41–43,54,69] demonstrated that combination therapy with ACT and APT did not confer a significant reduction in all-cause, non-vascular or mortality from unknown causes, over ACT alone.

Combination therapy was observed to significantly increase the risk of bleeding compared with ACT alone in two studies[41,73] (one randomised[41] and one non-randomised[73]), whereas one large non-randomised study[63] reported similar levels of bleeding with combination therapy, including triple therapy, compared with anticoagulation alone.[63] There is conflicting evidence regarding the effect of combination ACT plus APT compared with ACT alone on the risk of major bleeding with no randomised evidence reporting a significant increase in the risk with combination therapy compared with ACT alone.[39,41–43] Furthermore, the non-randomised studies reported inconsistent data, with two demonstrating higher rates of major bleeding with some combination therapy (VKAs plus aspirin)[54,69] over ACT alone, and lower bleeding rates with other combined therapy (VKA plus triflusal[54] or ximelagatran plus aspirin[69]), whereas the other study[73] reported an increased risk of major bleeding only with the highest dose of ACT plus APT compared with ACT alone. The rate of ICH reported in three randomised studies was very low and there was no evidence of a significantly increased risk of ICH with combination therapy over ACT alone.[39,42,43]

No significant increased risk in minor or non-severe bleeding was observed with combination therapy compared with anticoagulation alone,[39,40,42,43] whereas another small randomised study[41] reported a significant increase in the risk of minor/non-severe bleeding with combined therapy.

Although lower major adverse event rates were observed in three studies[39,41,54] (two randomised[39,41] and one non-randomised[54]) with combination therapy for the composite end points of severe bleeding, non-fatal stroke, TIA, SE and vascular death,[39] non-fatal stroke, TIA, SE, and vascular death,[39] embolism, stroke, AMI, and vascular death,[39] SE and death,[41] and stroke, systemic/coronary ischaemic events, AMI and mortality,[54] and all ischaemic events[54] than with anticoagulation alone, the difference between ACT plus APT and ACT alone was not significantly different in the two randomised studies.[39,41] Combination therapy conferred a significantly increased risk of the composite end point of stroke, SE and vascular death, compared with ACT alone, in one randomised study.[43]

Not all the randomised studies were of good quality. The mean duration of the studies varied from as low as 22 days[40] to 3.5 years,[42] with a sample size ranging from 43 patients[40] to 1209,[39] and compared an antiplatelet agent (aspirin, clopidogrel, triflusal) added to an anticoagulant agent (warfarin, acenocoumarol, fluindione) with anticoagulant alone (or ACT plus placebo). Most studies furnished clear information on the randomisation design and method; however, the majority undertook therapies in an open-label fashion.[39,42,43] No study reported a robust, randomised comparison in a high-risk AF population (with a specified $CHADS_2$ score of ≥ 2) between combined therapy of ACT targeting a standard therapeutic INR target of 2.0–3.0 plus additional APT, and ACT alone (target INR 2.0–3.0). Only one study[41] compared fluindione (target INR 2.0–2.6) plus additional aspirin with fluindione plus placebo (target INR 2.0–2.6) in a high-risk AF population. With a mean follow-up of 0.84 years and premature termination of the trial because of slow recruitment, the study results were less than adequate to be generalisable. Other studies investigated different doses of anticoagulant plus antiplatelet to anticoagulant alone in patients at variable (or unspecified) stroke risks.

The quality of those studies that reported non-randomised comparisons was generally poor. The sample size in these studies varied from 228 patients[59] to 118,606,[63] with follow-up periods of between 8 weeks[62] and 7.2 years.[52,61] Most studies were retrospective in nature, with patient data identified from a register of records, and with no or unclear information on blinding of assessors. APT was used at physicians' discretion in most studies, clearly indicated for cardiovascular diseases in a few, or for specific reasons which were not reported in others. The time of antiplatelet administration also varied across the studies or was not clearly specified.

Quality assessment of included studies was undertaken for this review. However, given the issues around heterogeneity between included studies, it was felt that extensive reporting of quality had little meaning in the context of this review. Therefore, in the results section, only summary tables of quality are provided (see *Tables 5* and *7*, and *Appendix 6*).

Methodology and issues

Several issues regarding methodological and clinical heterogeneity were encountered during the course of the review. A few are outlined in the following sections.

Population

The review aimed to assess the clinical benefit of combined therapy with ACT plus APT over ACT alone on vascular events in a population at high risk of stroke, with high risk determined either by history of AMI with PCI with or without stent, or having a $CHADS_2$ score of ≥2. However, not all studies identified such a population.

Risk of stroke

None of the included studies reported data for a high-risk population with a $CHADS_2$ score of ≥2. Those studies that evaluated stroke risk according to $CHADS_2$ score failed to report the outcomes for each $CHADS_2$ score category separately (high, moderate and low risk, respectively).[50,72]

Of the five studies that reported randomised comparisons, three[39,41,43] specified a high-risk AF population. However, the definition of high risk varied across the studies. None of the included studies specified diabetes mellitus as one of their stroke risk assessment criteria (diabetes mellitus being one of the risk score criteria of the $CHADS_2$ scheme). Of those that reported non-randomised comparisons, the majority did not specify the stroke risk of the sample, whereas the definitions of high risk varied across the studies in those that specified stroke risk.[50,55,58,64,65,72,73]

Study setting

Almost all non-randomised studies were conducted in hospital patients. This could have included more frail patients with multiple comorbidities that might place them at a higher risk for events and, therefore, would make the results from such studies less generalisable to a wider population.[51]

Of the studies reporting non-randomised data, six were based on reviews of hospital records.[56–58,60,61,63] Of these, one was a large study[63] on 118,606 patients over a mean follow-up of 3.3 years. It is important to note that such studies are at high risk of selection bias with less information on ethnicity and dosage and prone to poor documentation.[95] Results from these studies, therefore, need to be considered with caution.

Valvular diseases

Studies of patients with valvular diseases were included in the review. Those studies that included patients with valve replacements or mechanical heart valves were, however, excluded, despite the fact that this population is considered to be at high risk of stroke, because of different clinical target of anticoagulant INR range. If a study did not specify that subjects with valvular replacements were excluded, it was not excluded. For this reason, the studies by NASPEAF,[39] SPAF III[43] and Hansen *et al*.[63] were included in the review.

Intervention and comparator

The review was aimed at investigating combined ACT plus APT in comparison with ACT alone (plus placebo), with the dose of ACT adjusted to target the recommended INR range of 2.0–3.0 in both study arms.

Types of therapies

The type of both ACT and APT varied across the studies. Of the included randomised studies, three[40,42,43] reported data for warfarin therapy in different regimes in combination with different APT (aspirin, triflusal, clopidogrel). Of the remaining two RCTs, the FFAACS[41] study reported data for fluindione (ACT) and the NASPEAF study[39] assessed acenocoumarol (ACT) in combination with triflusal (APT). Both fluindione and triflusal are not known to be widely used in Europe and the UK. There was no further evidence available on these technologies.

Of those reporting non-randomised data, 14 studies reported data on warfarin in various regimes combined with an APT. Bover *et al*.[54] reported data for acenocoumarol plus triflusal, an APT that is not known to be widely used in the UK or Europe. This study[54] included a majority of patients enrolled in the NASPEAF trial.[39] The PETRO study[73] reported non-randomised data for dabigatran plus aspirin compared with dabigatran alone. No further evidence was available for this comparison. Ximelagatran was investigated in the two SPORTIF studies[64,65] and their six[66–71] supporting post hoc analyses. The AMADEUS study[72] did not specify the specific ACT (idraparinux or VKA) used in the comparison of ACT plus aspirin compared with ACT alone, whereas another study failed to identify the ACT.[58] Three studies did not report the name of the APT in the study.[52,59,60]

Dosage

Only two[40,41] of the five included randomised studies investigated ACT with the recommended target INR range of 2.0–3.0 in both study arms. Both studies were conducted on a small sample size ($n = 43$,[40] $n = 157$[41]) over a short period of follow-up. One did not specify either the stroke risk or the sample size calculations for the study.[40] The FFAACS study[41] was terminated early because of slow recruitment, which might have resulted in an overestimation of therapeutic efficacy.[96] Most studies reporting non-randomised comparisons reported the dosage of both therapies. Most studies reporting data for patients on warfarin specified the target INR of 2.0–3.0 in both study arms.[51,53,57,59,61,62,64,65] However, data from many of these did not add further information to the RCT data. The reasons for non-inclusion of data from these studies have been reported in *Appendix 7*.

Previous antithrombotic therapy

Of the randomised studies, two[41,43] of the included studies consisted of an anticoagulant-experienced population. Two other included RCTs[39,40] did not report this information and one[42] specified an anticoagulant-naive population. The majority of non-randomised studies also reported a population with a history of antithrombotic medication,[53–55,58,59,61,63,69,72,73] whereas others did not report this information. Such a population group might have potential implications of lower event rates because of patients' tolerance to an ACT in comparison with those who have no prior experience of ATT.

Outcomes

The review aimed to assess the benefit of combined therapy over ACT alone on vascular events in a high-risk AF population.

The primary outcome measures assessed were stroke, TIA, SE, the composite end point of SE and stroke, MI, vascular death along with secondary outcomes of all-cause mortality, bleeding events and composite end point consisting of various primary outcomes. Composite end points of stroke and SE were not specified in the review protocol; however, it was considered clinically relevant and reported in a considerable number of included studies and, therefore, was agreed to be reported in the review. The review protocol also specified in-stent thrombosis, revascularisation procedures and quality-of-life outcome measures; however, none of the included studies was found to report these events.

Outcome definitions

The review protocol specified definitions for each of the outcomes, which were broadly comparable with those specified in individual included studies. However, many studies failed to provide precise definitions of the outcomes.

Stroke, symbolic embolism, composite of stroke/systemic embolism, transient ischaemic attack, acute myocardial infarction and composite events

The majority of the included studies did not report a significant difference in event rates between the patients on combined therapy compared with those on ACT alone. Of the studies reporting randomised comparisons, one[43] reported a statistically significant higher risk of events in the combined therapy arm compared with ACT alone for the number of stroke events, composite of SE or stroke, and composite of stroke, SE and vascular deaths. However, the study compared warfarin [with a lower than recommended target INR range (1.2–1.5)] in combination with aspirin 300 mg with warfarin alone, targeting an INR of 2.0–3.0 in high-risk patients with AF in an open-label RCT with no blinding.[43] The population risk criteria in this study did not include diabetes mellitus, contrary to the current established stroke risk schemes such as $CHADS_2$.[27] Furthermore, the NASPEAF RCT[39] reported fewer events of composite of non-fatal stroke, TIA, SE and vascular death in combined therapy arm than in patients on acenocoumarol alone in both intermediate- and high-risk patients.[39] The INR range of acenocoumarol was below the recommended target of 2.0–3.0 in this study and established stroke risk assessment schemes were not used.

Risk of these events varied across the studies that reported non-randomised comparisons with low event rates and confounding of results by indication of APT.

Mortality: all cause and vascular

Most studies did not report a significant difference in mortality rates between the two therapy groups. Of the studies reporting randomised comparisons, only one study[39] reported a significantly lower rate of vascular death in patients on combined acenocoumarol plus triflusal than in those with acenocoumarol alone in either high- or low-risk patients. However, the low event rates in the study warrant cautious interpretation.[39] Non-randomised evidence for mortality was not free from bias, as evident from the previous sections. Therefore, it is difficult to deduce the benefits of combined ACT plus APT compared with ACT alone on mortality from the evidence available.

Bleeding

Significant differences in bleeding rates were not reported in the majority of the included studies. Only one RCT[41] reported significantly higher rates of bleeding in the combined therapy arm than with fluindione plus placebo.[41] However, the trial was prematurely terminated because of a small sample size with slow recruitment of patients ($n = 157$), resulting in a low study power to detect a meaningful effect of combined therapy on embolic events. Non-randomised evidence from one study[69] reported a larger number of bleeding events in the combined therapy group of warfarin plus aspirin than with warfarin alone. However, these groups were not evenly distributed and indication of aspirin for patients with CAD confounded the results.

Strengths and limitations

Strengths of the assessment

- Studies included in the assessment consisted of both randomised and non-randomised comparisons in an attempt to investigate all the available evidence around the subject.
- A comprehensive search strategy was undertaken encompassing all relevant databases.
- Robust review methodology was used.

Limitations of the assessment

- It was originally intended that an IPD analysis would be undertaken to specifically address the effect of APT added to ACT (compared with ACT alone) on various outcomes (including time to first vascular event/first major haemorrhage or clinically relevant bleeding/death and time within therapeutic INR range) (see *Appendix 1* and *Chapter 2*, *Changes to protocol*). Predefined subgroup analyses were to be developed to possibly include stent type; warfarin-naive versus warfarin-experienced subjects; short- and long-term outcomes; patients with diabetes mellitus; and $CHADS_2$ score ≥ 2 and < 2. However,

it became clear from the range of included studies that the methodological heterogeneity between studies, the clinical heterogeneity within and between studies, and the relatively small number of events was against such analyses being able to appreciably add to the findings of the review. To aid explanation, we draw the reader's attention to *Table 27*. This table summarises the key features and findings of the included studies grouped by similar intervention and comparator. Examining the section of the table containing the five studies that investigated combination ACT plus APT compared with ACT alone reveals that the intervention and comparator regimens were heterogeneous for both elements and, furthermore, the study designs were a mix of randomised and non-randomised comparisons. As with aggregate patient data meta-analysis, clinical and methodological study homogeneity are still overriding considerations prior to undertaking IPD meta-analyses and, thus, it was not an option to pool data across all studies in this case. Only two of the studies[67,69] had similar intervention/comparator characteristics and these were the same non-randomised comparison where aspirin was added to warfarin therapy based on clinical indication. Thus, as mentioned previously in this report, the treatment comparison in these studies was confounded by indication and IPD meta-analyses would therefore also be confounded. Where IPD analysis might have been beneficial is in possibly revealing data on outcomes previously unreported for a given study. In the current example, the greatest potential for this was with the two non-randomised comparisons with similar intervention/comparisons or for the outcome of TTR for all warfarin/aspirin studies. However, the utility of this was limited given the aforementioned limitation of combining data across studies. Similar issues also affected the value of IPD analyses for other intervention/comparator combinations (see *Table 27*). Thus, although the benefits of an IPD approach are well recognised[97] in the current report, the approach offered limited advantage. These issues were discussed with the NIHR and with their agreement it was decided not to undertake the planned the IPD analysis. As such, some aspirational aspects of the current work could not be achieved.

- Individual participant data analysis could not be undertaken for various reasons. Included studies reported low event rates, with methodological heterogeneity and ambiguity along with the fact that it was very difficult to identify studies with similar study designs, population characteristics, intervention and comparator therapies, and outcome measures. There is paucity of directly relevant randomised evidence to undertake a meta-analysis for the merits of one technology over another.
- The evidence was such that three stages of study selection were required, with one of these stages being unforeseen. With hindsight, this process might have been more efficiently achieved.
- Although the review initially aimed to identify high-risk patients, none of the included studies specified a high-risk group as per the established stroke risk assessment criteria. Studies were also included if stroke risk was not specified. This might have introduced studies with patients at a lower risk of stroke.
- It was intended to include only those studies that reported data for patients on combined ACT plus APT with a target INR range for ACT of between 2.0 and 3.0. However, this criterion could have been too restrictive; therefore, those studies in which no INR range was specified were also included, as it could not be ruled out that the appropriate INR was utilised.

Ongoing studies

Given the advent of novel oral anticoagulants, the direct thrombin inhibitors (e.g. dabigatran) and factor Xa inhibitors (e.g. apixaban, rivaroxaban and endoxaban), members of the steering committee are aware of planned post hoc non-randomised comparisons, between ACT plus APT and ACT alone, for the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY),[21] the Apixaban for Reduction In STroke and Other ThromboembolLic Events in Atrial Fibrillation (ARISTOTLE)[22] and the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF).[23] Two members from the steering committee are also the co-authors of the non-randomised comparison between ACT plus APT compared with ACT only in the post hoc analysis of the AMADEUS study,[72] which was published after the search strategy of the current review. Therefore, it is not included in this assessment.

Implications for future research

It is clear from the results of this systematic review that there are not sufficient data from the five randomised comparisons and 18 non-randomised comparisons to conclude whether or not there are high-risk patients with AF who would benefit from a reduction in vascular events with combined therapy of anticoagulation and APT compared with ACT alone.

Given the paucity of data, and the clinical and methodological heterogeneity encompassed in the studies from which the data comes, an individual participant data analysis is unlikely to prove beneficial. Likewise, it is recommended that a cost-effectiveness analysis at this point would be premature.

Given the absence of ongoing trials addressing the benefit of anticoagulation plus APT compared with anticoagulation alone in patients with AF at high-risk of TEs, it is recommended that a definitive prospective RCT needs to be undertaken. Any future trial would need to consider the following issues:

1. The population would need to be clearly defined. This would mean taking into account the different risk stratification scores, which currently exist in order to allow clinicians and policy-makers to interpret any findings within their specific health economy. Any future study should consider including a population at high risk of atherosclerotic coronary artery and other vascular events (following ACS ± stenting) and those patients at high risk of AF-mediated TEs.
2. The intervention would need to be clearly defined. There are currently data available from studies utilising different classes of drugs with ongoing post hoc analyses becoming available for new classes of both anticoagulant and antiplatelet agents. Any future study would need to address these potential class effects. From the UK context, at the time of writing, any future trial should compare adjusted-dose warfarin (INR 2.0–3.0) plus aspirin (75–325 mg) with adjusted-dose warfarin (INR 2.0–3.0). However, given the emergence of newer anticoagulation agents (dabigatran, rivaroxaban and apixaban) this prioritisation may need to be revisited in the future to reflect current best clinical practice.
3. Any future study should include a health economic analysis.
4. The comparator group would need to receive the same ACT as the intervention group; thus, if the anticoagulant under investigation was a VKA, then the comparator group should have the same INR target as the intervention group. Similarly, achieved INRs in terms of therapeutic time in range should be reported for both groups.
5. All outcomes would need to be clearly defined in order to allow clinicians and policy-makers to interpret any findings within their specific health economy.
6. All outcomes would need to be independently validated in line with international definitions.
7. Analysis of outcomes would need to be undertaken in line with contemporary methods of assessing net clinical benefit.
8. Duration of follow-up needs to be sufficient to allow (1) confidence that the findings would reflect real world utilisation of the technologies and (2) a reasonable number of events. This will obviously be dependent on sample size, but should be at least 1 year.

Conclusion

This systematic review identified five randomised and 18 non-randomised studies that compared treatment with anticoagulation and APT with treatment with ACT alone in patients with AF. These studies were generally of poor quality, utilised different anticoagulant and APTs, investigated different populations of patients in terms of risk, had different follow-up periods and used different outcome measures, with various definitions of these outcomes.

The data from these studies are not sufficient to conclude whether or not there are patients with AF in whom the addition of an antiplatelet agent to an anticoagulant is warranted in terms of benefit from reduction of vascular events compared with an increased risk of bleeding.

It is recommended that a definitive prospective RCT is undertaken, preferably in a population at high risk of atherosclerotic coronary artery and other vascular events in addition to being at high risk of AF-mediated TEs, utilising interventions and comparators that include current and emerging ACT and APT strategies, which also takes into account the findings of this review.

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Contribution of authors

Deirdre A Lane, joint principal investigator, contributed to the development of the protocol, study selection, data extraction and quality assessment, writing of the report and provided clinical input.

Smriti Raichand contributed to the development of the protocol, study selection, data extraction and quality assessment, and writing of the report.

David Moore contributed to the development of the protocol, provided methodological input, and contributed to study selection and writing of the report.

Martin Connock contributed to the development of the protocol and study selection (abstract screening).

Anne Fry-Smith, devised the search strategy and carried out the searches.

David Fitzmaurice, joint principal investigator, contributed to the development of the protocol, study selection, report writing and provided clinical input.

All authors provided input to the development of the review report, commented on various drafts of the chapters and contributed to their editing.

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Appendix 1 Final protocol

Research question

Is there a subgroup of high risk atrial fibrillation (AF) patients receiving anticoagulation therapy (ACT), in whom adding antiplatelet therapy (APT) can be justified in terms of the balance between reducing vascular events, without increasing bleeding?

Background

Both coronary artery disease (CAD) and AF are increasing in prevalence as a consequence of the improvements in survival due to advances in medical therapy and the ageing population. Epidemiological data suggests that the lifetime risk for development of AF is 1 in 4.[1,2] Further, between 30–40% of patients with AF have concomitant CAD,[3] and some of these patients may also require percutaneous coronary intervention (PCI) with stent implantation. Patients with AF and CAD are at increased risk of both stroke and further coronary events. An increasingly common antithrombotic management problem arises when faced with an anticoagulated patient with AF at high risk because of an acute coronary syndrome (ACS) or requirement for PCI with stent implantation, or because they have diabetes mellitus.[4]

For high risk AF patients receiving ACT the addition of APT may be expected to reduce the probability of a thrombotic event but may also increase the risk of haemorrhagic events.[5-7] Thus the main problem with combination antithrombotic therapy relative to ACT alone is an increased risk of bleeding. The choice between combination therapy or ACT alone depends mainly on clinical judgment about the balance of probabilities of thrombotic and haemorrhagic events and their relative severities. This balance may differ for various high risk categories of AF patients. Recent guidelines (Appendix I) recommend that combination antithrombotic therapy should be considered as a treatment option for certain AF patients (such as those in receipt of stents). Our scoping searches have failed to identify a systematic review of the evidence that could underpin these recommendations. This project aims to address this gap as there is a perceived existence of different subgroups of high risk AF patients. It is anticipated that access to individual person data (IPD) analysis will be undertaken to try to identify the relative effectiveness of ACT alone versus combination therapy in such groups.

Objective

To perform a systematic review of studies of AF patients receiving ACT, so as to compare the effectiveness of ACT alone with that of ACT plus APT. High risk patients of special interest include AF patients with previous myocardial infarction (MI) or ACS, those undergoing PCI and stent implantation, those with diabetes mellitus, and those with a $CHADS_2$ score ≤ 2.

Methods/design

Systematic review

Standard systematic review methodology will be employed consisting of searches to identify published literature, sifting and application of specific criteria to identify relevant studies, assessment of the quality of these studies and the extraction and synthesis of relevant data from them. These stages are described below.

(i) Search strategy

The following bibliographic databases will be searched using a broad strategy: Cochrane Library (to include the Cochrane Database of Reviews, DARE, HTA Database, and CENTRAL), MEDLINE (Ovid) 1950 onwards, MEDLINE in Process (Ovid), and EMBASE (Ovid) 1980 onwards. Searches will use a range of index and text words (see Appendix II for details)

Ongoing trials will also be sought in publicly available trials registers, such as ClinicalTrials.gov, NIHR Clinical Research Network Portfolio and Current Controlled Trials (see Appendix III for ongoing trials already identified).

(ii) Screening strategy

All studies with 'anticoagulation' and 'atrial fibrillation' (or equivalent) in the title or abstract will be identified from the search.

Titles (and abstracts where available) of articles identified by the searches will be screened by two reviewers for relevance to the review question. This process will be aimed at removing non-relevant studies. Hard copies of remaining studies will be acquired for assessment independently by two reviewers against the selection criteria for the review (see below). Discrepancy between reviewers will be resolved by discussion or by referring to a third reviewer. A record of all rejected papers and the reasons for rejection will be documented.

(iii) Selection criteria for identification and inclusion of studies

- **Patient group** AF patients aged ≥18 years. Studies with a patient population requiring ACT exclusively for indications other than AF (prosthetic heart valve, etc.) will be excluded.
- **Intervention group** ACT (various therapies) combined with orally administered APT agents (mono- or dual- therapy) (See Appendix IV for a list of specific anticoagulants and antiplatelet interventions). Only interventions employing therapeutic target INR ranges for atrial fibrillation (INR 2.0 to 3.0) will be included. For the purposes of mapping the evidence we will record studies of predominantly non-AF populations which nevertheless include subgroups of AF patients (see Appendix V).
- **Comparator group** Patients receiving ACT alone or ACT plus placebo.
- **Setting** Studies in any setting will be included.
- **Outcomes** Any vascular event including composite end points (for example all vascular events); all-cause mortality. Acceptable outcomes are listed in Appendix VI.
- **Study design** Randomised controlled trials (RCTs); non-randomised controlled trials; longitudinal and registry studies if exclusively AF patients. Data from RCTs that randomised patients to ACT alone versus ACT plus APT will be given precedence over other study designs. Studies comparing ACT alone to APT alone will be excluded.

(iv) Critical appraisal and synthesis strategy: data abstraction and quality assessment

Data abstraction and quality assessment of included studies will be conducted by one reviewer and checked by another reviewer in accordance with guidelines in Chapter 7 of the Cochrane Handbook for Systematic Reviews of Interventions.[8]

For each study, data will be sought in detail under explicit subheadings (see Appendix VII). Sufficient portions of non-English papers will be translated to facilitate this process.

The methodological quality of RCTs that randomised patients to ACT alone versus ACT plus APT will be assessed in terms of the randomisation process, allocation concealment (adequate, unclear, inadequate, or not used), degree of blinding, particularly of the outcome assessors, and patient attrition rate.[8] The risk of bias in studies will be summarised using Rev Man 5 risk-of-bias tool.[8] The quality assessment of the observational studies will use the CRD Checklist for cohort studies, case-control studies and case series.[9] We will consider the cohort studies for quality assessment using this checklist.

Individual patient data meta-analysis

All analyses will be performed following the intention-to-treat analysis. We will use the I^2 statistic to assess heterogeneity.[10]

The individual patient meta-analysis will specifically address the effect of ACT alone versus ACT plus APT on (i) time to first vascular event; (ii) time to first major haemorrhage or clinically relevant bleed; (iii) death; and (iv) time within therapeutic INR range. Depending on data availability, predefined subgroup analyses will be developed and may include the following: (i) stent type (bare metal vs drug-eluting); and (ii) warfarin-naïve vs warfarin-established subjects; (iii) short-term and long-term outcomes; (iv) patients with diabetes mellitus.; and (v) $CHADS_2$ score ≥ 2 and < 2.

Data will be requested either in electronic or paper form. A desired format and coding will be specified but trial authors may supply data in the most convenient way open to them, provided details of coding are included with the data. For defining adverse outcomes as major or minor, a Delphi technique will be employed using a list of all reported adverse outcomes. All contributors to the IPD will be sent a blinded list of these adverse outcomes for classification. All data emerging from this component of the work will be reviewed using the same criteria as other studies identified through the search strategy (see above).

Copies of the original data will be made to use in the analyses. Trial details and summary measures will be cross-checked against published articles by two reviewers. Consistency checks will be applied with any errors or inconsistencies discussed with the original triallist.

Methodological considerations

The scoping search has revealed a likely scarcity of RCTs that directly address the review question, especially with regard to the subgroups of special interest. We therefore have considered the methodological implications of including a wider variety of studies such as those in which the recruited population may have included some AF patients of whom a proportion received ACT alone or ACT plus APT. The problem with these types of study is that the patient groups compared are subject to severe selection bias and they do not yield a randomised comparison between the treatments. These considerations are detailed more fully in Appendix V.

When the potential sources of evidence have been obtained and categorised (i.e. mapped) an informed decision will be made regarding the appropriate and feasible analytical approach to be adopted given the time frame available. This decision will also depend on the availability of IPD. The steering group will be consulted on this decision.

Mapping exercise

It was discussed with the steering group whether to include only RCTs that directly compare ACT with combined therapy or to go beyond these and utilise the evidence by including a wider group of study designs and comparisons. It was discussed that the latter strategy would introduce confounding due to indication. The steering group decided to go beyond the scope of RCTs and include prospective observational studies and registries with an AF population receiving ACT, which might have a subgroup of patients on combined ACT plus APT. In order to make this a manageable process, it might be necessary to invoke a study characteristics cut-off. In order to inform this decision, it will be necessary to map the potentially relevant studies. Relevant studies will be identified from search results using criteria for population (AF), Intervention (ACT) and possibly other characteristics (e.g. comparator). This will be undertaken by two people independently. We will map the studies according to the study design, sample size and length of follow up, and avoid bias by ignoring the results. Based on this mapping exercise, a cut off point beyond the directly relevant RCTs will be decided.

Expected output of research

This systematic review will reveal the extent and quality of available evidence bearing on the potential harms or benefits of combination antithrombotic therapy over ACT alone for AF patients. It will also assess the amount of upcoming evidence from ongoing studies. This information can inform future research directions.

Should sufficient good quality evidence be available predictive models generated from our analysis of IPD could lead to identification of any AF patients receiving ACT that might benefit or be harmed from combination ACT plus APT. It is possible that the findings will not demonstrate either benefit or risk of ACT plus APT over ACT alone.

Project timetable and milestones

When the systematic review has mapped and categorised the weight and quality of available evidence, together with the anticipated upcoming evidence from ongoing trials, a decision about the direction and timelines for the project will be made by the whole team.

Appendix I

Clinical guideline for management of AF

Guidelines*	Risk definition[a]	Stent type[a]	Recommendations[b]	Follow-up
The UK NICE guidelines, 2005[11]	Does not address this topic – acknowledge that adding aspirin to warfarin increases bleeding		Individual assessment of the risk–benefit ratio in prescribing aspirin plus warfarin in patients with associated CAD	
ACC/AHA/ESC Guidelines, 2006[12]	AF + PCI or revascularization surgery		Aspirin (less than 100 mg/day) and/or Clopidogrel (75 mg/day) + Warfarin (INR 2.0–3.0)	Warfarin alone (in absence of a subsequent coronary event)
		BMS	Warfarin (INR 2.0–3.0) + Aspirin + (Clopidogrel ≥1 month)	Warfarin (INR 2.0–3.0) alone
		sirolimus-eluting stent	Warfarin (INR 2.0–3.0) + Aspirin + (Clopidogrel ≥3 months)	Warfarin (INR 2.0–3.0) alone
		paclitaxel-eluting stent	Warfarin (INR 2.0-3.0) + Aspirin + (Clopidogrel ≥6 months)	Warfarin (INR 2.0–3.0) alone
		selected patents	Warfarin (INR 2.0–3.0) + Aspirin + (Clopidogrel ≥12 months)	Warfarin (INR 2.0–3.0) alone
8th ACCP, 2008 guidelines[13]	AF + High stroke risk + ACS		Aspirin (<100 mg per day) or Clopidogrel (75 mg per day) + ACT (INR 2.0–3.0)	
ACC Guidelines, 2008[14]	AF + ACS + PCI + Low bleeding risk		Coumarins + Aspirin + Clopidogrel	
EHRA and EAPCI Guidelines, 2010[15]	AF + Elective PCI + moderate-high thromboembolic risk + low/intermediate haemorrhagic risk	BMS	Aspirin (75–100 mg/day) + Clopidogrel (75 mg/day) + Warfarin (INR 2.0–2.5) ≥1 month	Long term Warfarin (INR 2.0–3.0)
		-limus-eluting stent	Aspirin (75–100 mg/day) + Clopidogrel (75 mg/day) + Warfarin (INR 2.0–2.5) ≥3 months	Long term Warfarin (INR 2.0–3.0)
		paclitaxel-eluting stent	Aspirin (75–100 mg/day) + Clopidogrel (75 mg/day) + Warfarin (INR 2.0–2.5) ≥6 months	Long term Warfarin (INR 2.0–3.0)
	AF + ACS + PCI moderate-high thromboembolic risk + low/intermediate haemorrhagic risk	BMS/DES	Aspirin (75–100 mg/day) + Clopidogrel (75 mg/day) + Warfarin (INR 2.0–2.5) ≥6 months OR Clopidogrel (75 mg/day) [or Aspirin (100 mg/day)] + Warfarin (INR 2.0–2.5 – 12 months	Long term Warfarin (INR 2.0–3.0)
	AF + ACS + PCI + moderate-high thromboembolic risk + high haemorrhagic risk	BMS (avoid DES)	Aspirin (75–100 mg/day) + Clopidogrel (75 mg/day) + Warfarin (INR 2.0–2.5) ≥4 weeks OR Clopidogrel (75 mg/day) [or Aspirin (100 mg/day)] + Warfarin (INR 2.0–2.5 – 12 months	Long term Warfarin (INR 2.0–3.0)

APPENDIX 1

Guidelines*	Risk definition[a]	Stent type[a]	Recommendations[b]	Follow-up
AHA Updated Guidelines, 2010[16]	AF + PCI + high stroke risk ($CHADS_2$ >1) + low bleeding risk		Warfarin (INR 2.0–2.5) + Dual APT (Aspirin 75–100 mg/d + clopidogrel 75 mg/d) [plus proton pump inhibitor for gastro intestinal bleed]	
		BMS	Warfarin (INR 2.0–2.5) + Dual APT ≥1 month	
		sirolimus-eluting stent	Warfarin (INR 2.0–2.5) + Dual APT ≥3 months	
		paclitaxel-eluting stent	Warfarin (INR 2.0–2.5) + Dual APT ≥6 months	
	AF + PCI + high stroke risk ($CHADS_2$ >1) + high bleeding risk		Dual APT alone	
ESC Guidelines for Management of Artrial Fibrillation, 2010[17]	AF + Elective PCI + moderate-high thromboembolic risk + low/intermediate haemorrhagic risk (HAS-BLED 0-2)	BMS	1 month: VKA (INR 2.0–2.5) + Aspirin (≤100 mg/day) + Clopidogrel 75 mg/day)	Long term VKA (INR 2.0–3.0)
		DES	3 (-olimus group) to 6 (paclitaxel) months: VKA (INR 2.0–2.5) + Aspirin (≤100 mg/day) + Clopidogrel (75 mg/day) Up to 12 months: VKA (INR 2.0–2.5) + Clopidogrel (75 mg/day) [or Aspirin (≤100 mg/day) with PPI if indicated] OR Aspirin (100 mg/day)	Long term VKA (INR 2.0–3.0)
	AF + ACS + PCI + moderate-high thromboembolic risk + low/intermediate haemorrhagic risk (HAS-BLED 0-2)	BMS/DES	6 months: VKA (INR 2.0–2.5) + Aspirin (≤100 mg/day) + Clopidogrel (75 mg/day) Up to 12 months: VKA (INR 2.0–2.5) + Clopidogrel (75 mg/day) [or Aspirin (≤100 mg/day) with PPI if indicated] OR Aspirin (100 mg/day)	Long term VKA (INR 2.0–3.0)
	AF + Elective PCI + moderate-high thromboembolic risk + high haemorrhagic risk (HAS-BLED ≥ 3)	BMS (avoid DES)	2–4 weeks: VKA (INR 2.0–2.5 + Aspirin (≤100 mg/day) + Clopidogrel (75 mg/day)	Long term VKA (INR 2.0–3.0)
	AF + ACS + PCI + moderate-high thromboembolic risk + high haemorrhagic risk (HAS-BLED ≥3)	BMS (avoid DES)	4 weeks: VKA (INR 2.0–2.5) + Aspirin (≤100 mg/day) + Clopidogrel (75 mg/day) Up to 12 months: VKA (INR 2.0–2.5) + Clopidogrel (75 mg/day) [or Aspirin (≤100 mg/day) with PPI if indicated] OR Aspirin (100 mg/day)	Long term VKA (INR 2.0–3.0)

* Acronyms used in this column: ACC: American College of Cardiology: ACCP: American College of Chest Physicians: AHA: American Heart Association: EAPCI: European Association of Percutaneous Cardiovascular Interventions: EHRA: European Heart Rhythm Association: ESC: European Society of Cardiology: NICE: National Institute for Health and Clinical Excellence.

a Acronyms used in this column: ACS: Acute Coronary Syndrome: AF: Atrial Fibrillation: BMS: Bare Metal Stent: DES Drug Eluting Stent: HAS-BLED: bleeding risk score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (> 65 yrs), drugs//alcohol concomitantly): PCI, percutaneous intervention.

b Acronyms used in this column: APT: Antiplatelet Therapy: CAD Coronary Artery Disease: INR: International Normalised Ratio: VKA Vitamin K Antagonists.

Appendix II

Details of search strategy

Search words: "anticoagulants", "vitamin-K antagonists", "coumarins", "heparin", "low-molecular weight heparin", "hirudins", "oral thrombin inhibitors", "antiplatelets", "aspirin", "clopidogrel", "ticlopidine", "dipyridamole"; and the patient group: atrial fibrillation, e.g. "atrial fibrillation", "myocardial infarction", "acute coronary syndromes", "percutaneous coronary intervention", "coronary stenting". Although studies which include combined anticoagulant and antiplatelet therapy will be sought, terms representing the latter will not be included in the search strategy in order to allow a broader search to be undertaken.

No filter for study designs will be used. The search strategy will be developed in consultation with an information specialist and adapted to the individual databases. Restrictions on publication language or date will not be applied.

In addition, abstract books from key national and international cardiology (British Cardiac Society, American College of Cardiology, European Society of Cardiology, American Heart Association), and stroke (International Stroke Conference, American Stroke Association) conferences from 2009 onwards will be hand-searched. We will seek additional trials from key experts in the fields of AF, ACS and PCI/stenting. Unpublished studies that are identified will be considered in a similar way to published studies.

Appendix III

Ongoing studies

Study (Stage)	Population	Intervention	Comparator	Outcome	Follow Up	Study design	Comments	Available
WOEST (Currently recruiting)	N = 496; Age: >18 yrs; At least one year of Anti-Coagulant Therapy (AF, Valvular diseases …); Indication for PCI	Combination oral anticoagulation therapy and clopidogrel 75 mg/d	Triple therapy (oral anticoagulation therapy + clopidogrel 75 mg/d + aspirin 80 mg/d)	Primary: composite of minor, moderate, and major bleeding Secondary: individual componenets of the primary end point: minor bleeding, moderate bleeding, and major bleeding and also the safety and points: the combined event of death myocardial infarction, stroke, systematic embolization, target vessel revascularization, and stent thrombosis	1 year	Open Label Randomised Controlled Trial	The interventions and comparators are not of interest	http://www.clinicaltrials.gov/ct2/show/NCT00769938?term=WOEST&rank=1
ISAR-TRIPLE (Currently recruiting)	N = 600; Age ≥18 Yrs; Patients with an indication for oral anticoagulation and a DES implantation.	6 weeks triple therapy with Aspirin, Clopidogrel, Oral Anticoagulation	6 months triple therapy with aspirin, clopidogrel and oral anticoagulation	Primary: Composite of death, myocardial infarction, definite stent thrombosis, stroke or major bleeding Secondary: Ischemic complications (composite of cardiac death, myocardial infarction, stent thrombosis or ischemic stroke), and Bleeding complications (Major bleeding)	9 months	Open Label, Active Control Randomised Controlled Trial	The interventions and comparators are not of interest	http://www.clinicaltrials.gov/ct2/show/NCT00776633?term=isar-triple&rank=1

Study (Stage)	Population	Intervention	Comparator	Outcome	Follow Up	Study design	Comments	Available
RELY (Completed)	N = 18,113; Patients with non-valvular atrial fibrillation (AF), at moderate to high risk of stroke, or systemic embolism with at least one additional risk factor (i.e. previous ischemic stroke, TIA, or systemic embolism, left ventricular dysfunction, age ≥75 years, age ≥65 with either diabetes mellitus, history of coronary artery disease or hypertension)	Dabigatran (110 mg/150 mg)	Warfarin (adjusted Dose)	Primary: Incidence of stroke (including hemorrhagic) and systemic embolism Secondary: Incidence of stroke (including hemorrhagic), systemic embolism, all death Incidence of stroke (including haemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction, or vascular deaths (including deaths from bleeding)	2 years	Prospective, Multi-centre, Parallel-group, Non-inferiority Randomised Controlled Trial	Might not be of use as Intervention is not of interest	Connolly, Ezekowitz et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;**361**:1139-51. Epub 2009 Aug 30.
ARISTOTLE (active, not recruiting)	N = 18,183; Males and females ≥18 yrs with AF and one or more of the following risk factors for stroke: Age ≤75, previous stroke, TIA or Systemic Embolism, Symptomatic congestive HF or left ventricular dysfunction with LVEF ≤40%, Diabetes mellitus or hypertension requiring pharmacological treatment	Apixaban (5.0 mg twice daily)	Warfarin (INR 2.0–3.0)	Primary: confirmed stroke or systemic embolism Secondary: confirmed ischemic stroke, hemorrhagic stroke, systemic embolism, al cause death		Active Controlled, Randomized, Double-Blind, Parallel Arm study	The interventions and comparators are not of interest	http://clinicaltrials.gov/show/NCT00412984

Study (Stage)	Population	Intervention	Comparator	Outcome	Follow Up	Study design	Comments	Available
ENGAGE-AFTIMI48 (Currently recruiting)	N = 20,500; Age ≥21 years; male or female; history of documented AF within the prior 12 months; moderate to high risk of stroke, as defined by CHADS2 index score of at least 2	DU-176b (High Dose) DU-176b (Low Dose)	Warfarin	Primary: stroke and systemic embolic events Secondary: composite clinical outcome of stroke, SEE, and all-cause mortality; major bleeding events	24 Months	Randomized, Double-Blind, Double-Dummy, Parallel Group, Multi-Center, Multi-National Study	The interventions and comparators are not of interest	http://www.clinicaltrials.gov/ct2/show/NCT00781391?term=ENGAGE-AF&rank=1
ROCKET-AF (Ongoing, not recruiting)	N = 14,000; Male and female patients; Age ≥18 years; documented atrial fibrillation on 2 separate occasions with 1 year before screening; History of a prior stroke, transient ischemic attack or non-neurologic systemic embolism believed to be cardiac in origin, OR at least two of the following risk factors: HF, Hypertension, Age ≥ 75 years, Diabetes mellitus	Rivaroxaban	Warfarin: INR of 2.5 (range 2–3) + Rivaroxaban placebo	Primary: Composite of major and non-major clinically relevant bleeding events; any stroke or non-CNS systemic embolism Secondary Outcome:Each category of bleeding events, and adverse events; composite of stroke, non-CNS systemic embolism, and vascular death	32 Months	prospective, randomised, double-blind, double-dummy, parallel-group, active-control, non-inferiority study	The interventions and comparators are not of interest	http://www.strokecenter.org.trialDetail.aspx?tid=951
AVERROES (Completed)	N = 5600; AF, Age ≥50 years; At least 1 risk factor for Stroke; Have failed/ are unsuitable for Vitamin K Antagonist Treatment	Apixaban (Double-Blind Phase); Apixaban (Long-Term Open-Label Phase)	Acetylasalicylic Acid (ASA): Placebo Comparator	Primary: time (days) from first dose of study drug to first occurrence of unrefuted ischemic stroke, hemorrhagic stroke or systemic embolism Secondary: the time (days) from first dose of study drug to first occurrence of unrefuted Ischemic stroke, hemorrhagic stroke, systemic embolism, myocardial infarction, or vascular death	36 months	Randomised, double-blind, parallel-group, active-control, study	The interventions and comparators are not of interest	http://clinicaltrials.gov/ct2/show/NCT00496769?term=AVERROES&rank=1

APPENDIX IV

List of Interventions

Anticoagulants:

- oral anticoagulants (warfarin, acenocoumarol, and phenindione),
- heparins,
- low-molecular-weight heparins,
- hirudins,
- idraparinux,
- direct oral thrombin inhibitors (ximelagatran, dabigatran).

Antiplatelets:

- aspirin,
- clopidogrel,
- ticlopidine,
- dipyridamole,
- triflusal.

Appendix V

Methodological considerations on types of study that might be considered for analysis

In order to systematise our approach to gathering relevant studies, below we categorise the potential sources of available and future evidence. This is done according to study design and the risk of bias in the comparison of ACT alone versus ACT plus APT. When these sources have been obtained and categorised (i.e. mapped) an informed decision can be made regarding the weight and quality of evidence that can inform the analytical approach to be adopted given the time frame available. This decision will also depend on the availability of IPD.

The following types of study might potentially yield information for the review:

1. Randomised control trials (RCTs)

RCTs with an exclusively AF population:

(i) ACT alone versus ACT plus APT (Ideal RCT)

An ideal study design will be an RCT in which the population is a group of AF patients, with or without a previous ACS, or experience of PCI (± stent), or with or without diabetes. This population would be randomly assigned to either ACT alone or ACT plus APT. This will allow randomised comparison of effects of the therapies. It will directly address the benefits and risks of compared treatments in AF patients including those categorised within the subgroups of special interest. It may provide aggregate data for the AF subgroups of particular interest or these subgroups can be analysed using IPD if this is available.

(ii) RCTs comparing two different ACTs

These studies may have some participants that receive APT (in addition to ACT) either from the start of the trial or beginning at some time during the trial. A post-hoc subgroup analysis comparing outcomes for ACT alone versus ACP plus APT patients could be undertaken.

It is possible, but unlikely, that aggregate data comparing ACT alone versus ACT plus APT will be in the public domain, so that availability of IPD will be a likely prerequisite determining the potential utility of these studies. Compared patients (ACT versus ACT plus APT) might have been randomised into any arm of the trial. Irrespective of whether the comparison is restricted within an arm (i.e. all patients receive the same ACT) or across arms (patients may receive different ACTs) the comparison lacks the strength of randomisation. Furthermore since patients who receive APT will be those with particular clinical indication that warranted this treatment the comparison will be systematically biased by selection. To partially mitigate the problem of selection bias it might be possible to identify ACT-only patients with the same indication as those that received APT but who did not receive APT. An alternative approach would be to stratify the combination therapy patients according to risk factors and then restrict comparison with ACT-only patients within the same strata. Bearing in mind these drawbacks it is unlikely these trials will provide robust information.

RCTs enrolling participants only some of whom are AF.

(i) RCT comparing two ACTs (e.g. warfarin versus another ACT)

In these studies, the primary indication for anticoagulant therapy may not necessarily be AF. Possibly a post-hoc subgroup analyses of AF from such trials may provide data for the comparison of interest and within the patient categories of special interest if some of these patients receive ACT as well as APT. As with a (ii) above it is unlikely aggregate data will be available and IPD would be a prerequisite; again the comparison between treatments will be non-randomised and systematically at risk of selection bias.

2. Non-randomised studies

Non-Randomised studies might exist with the following characteristics:

a. Longitudinal studies (prospective or retrospective)

(i) Prospective studies of AF patients given a particular ACT, some of whom at some time additionally receive APT

These studies by design may have allowed at recruitment the entry of AF patients receiving ACT alone and others receiving combination therapy. It is likely IPD would be required from these. For reasons described above a comparison of outcomes between these two groups would be subject to selection bias because of the indication that led to the adoption of the combination therapy. Alternatively the combination therapy patients may have started on APT during follow up and outcomes would be relevant only from that time rather than from the time of recruitment. Again stratification by risk factors and analysis within strata, or identification of ACT-only patients with matched indication but received no additional APT, might mitigate selection bias to some extent.

(ii) Prospective longitudinal studies that recruit AF patients receiving various ACTs

The same considerations apply as for 2.a*(i)*

(iii) Prospective longitudinal studies of patients receiving ACT

Subgroup analyses from studies with patients on ACT may provide information given that some of these may be AF patients and some might receive additional APT by indication. Again these studies will be unlikely to provide aggregate results for patient groups of interest and their potential utility would depend on IPD availability. Any comparisons between treatments will again be highly susceptible to selection bias.

b. Registries of AF patients on Antithrombotic therapy

Registries may collect a variety of detailed information on different categories of patients according to therapy and condition. These might provide information on outcomes for the patient subgroups of special interest. The comparison of ACT alone versus ACT plus APT would again lack the strength of randomisation and would be subject to selection bias by indication; again this might be partially mitigated if we find sub-populations very similar to each other in their characteristics. A further selection bias may be expected from registry data because of unbalanced coverage of patient categories, because of this it is possible that registry data may be insufficiently complete for data extraction to be worthwhile.

Potential advantages and disadvantages of using studies allowing non-randomised comparisons

Advantages of including non-randomised comparisons in a review:

- increase in power
- some consider this better reflects outcomes for real-world patients as distinct from more narrowly defined patient groups that are enrolled in RCTs.

Disadvantages include:

- difficulties in identifying studies and registries (search strategies and existing filters have not been extensively developed);
- inherent weaknesses from lack of control over compared treatments and compared populations (especially susceptibility to selection bias)

- probable inability to obtain IPD from all identified studies within the time frame of the project (raising a potential problem analogous to publication bias)
- difficulties in assessing the quality of the data and in cleaning it up.

Potential analytical strategies include:

I. Pool the randomised and non-randomised comparisons together. However, this is discouraged in Cochrane Handbook for Systematic Reviews of interventions.[8]
II. Analyse and present randomised and non-randomised data separately.
III. Select suitable non-randomised comparisons in some manner based on quality or other study characteristics (e.g. if larger than the included RCTs; if prospective ; if data available for subgroups of special interest).
IV. Use non-randomised comparisons as a form of sensitivity analysis for the randomised comparisons.

Appendix VI

Outcome measures

Primary outcome measures

Vascular events:

- non-fatal and fatal ischemic stroke,
- transient ischemic attack,
- systemic embolism (pulmonary embolism, peripheral arterial embolism),
- myocardial infarction,
- in-stent thrombosis,
- vascular death (from any of the always mentioned vascular events).

Secondary outcome measures

1. all-cause mortality;
2. bleeding: defined as follows according to the International Society of Haemostasis and Thrombosis:[18]
   i. *Major bleeding events* if (i) fatal bleeding and/or (ii) symptomatic or in a critical area or organ, such as intracranial, intraspinal, intraocular, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin level of 2 g/dl (1.6 mM) or more; or leading to a transfusion of two or more units of whole blood or red cells].
   ii. *Clinically relevant non-major bleeding events* will be defined as acute or sub-acute clinically overt bleeding that does not satisfy the criteria of major bleeding and that leads to either (i) hospital admission for bleeding or (ii) physician guided medical or surgical treatment for bleeding or (iii) a change in antithrombotic therapy.
   iii. *Minor bleeding* events will be defined as all acute clinically overt bleeding events not meeting the criteria for either major bleeding or clinically relevant non-major bleeding.[18]
3. health-related quality of life;
4. major adverse events (composite of all-cause mortality, non-fatal MI and stroke);
5. revascularisation procedures (e.g. percutaneous coronary intervention, CABG, embolectomy);
6. percentage time in INR range (where available).

Appendix VII

Data abstraction

For each study, data will be sought under the following broad headings:

- antithrombotic regimens employed (anticoagulant ± antiplatelet(s) or placebo);
- type of antithrombotic therapy used and dose;
- target INR values employed;
- indication for antithrombotic therapy (AF ± ACS or stent implantation);
- country of origin;
- study design;
- sample size;
- patient inclusion and exclusion criteria;
- patient characteristics (age, sex, type and duration of AF, anticoagulant-naïve or -established);
- comparability of patients between different arms (for RCTs and non-randomised trials);
- primary outcome measures (all vascular events, including MI, ACS, ischaemic stroke, TIA or systemic embolism, cardiovascular death);
- secondary outcome measures (all-cause mortality, quality of life, adverse events, major and minor bleeding; revascularisation; time within therapeutic INR range);
- length of follow-up;
- statistical methods employed;
- effect sizes.

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Appendix 2 Literature search strategies

Ovid MEDLINE(R) 1950 to September week 1 2010

1. exp Anticoagulants/ (159,888)
2. (anticoagulant$ or anticoagulation).mp. (69,316)
3. (anti coagulant$ or anti coagulation).mp. (1193)
4. (warfarin or acenocoumarol or coumadin or coumarin or phenprocoumon or sintrom or sinthrome or jantoven or marevan or waran or nicoumalone or dicoumarol or dicumarol).mp. (24,778)
5. (phenindione or dabigatran or ximelagatran or apixaban or rivaroxaban or edoxaban or azd0837 or ly517717 or ym150 or betrixaban or idraparinux).mp. (1606)
6. or/1-5 (182,359)
7. atrial fibrillation.mp. (33,393)
8. 6 and 7 (4989)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 27 September 2010

1. (anticoagulant$ or anticoagulation).mp. (1463)
2. (anti coagulant$ or anti coagulation).mp. (55)
3. (warfarin or acenocoumarol or coumadin or coumarin or phenprocoumon or sintrom or sinthrome or jantoven or marevan or waran or nicoumalone or dicoumarol or dicumarol).mp. (1003)
4. (phenindione or dabigatran or ximelagatran or apixaban or rivaroxaban or edoxaban or azd0837 or ly517717 or ym150 or betrixaban or idraparinux).mp. (91)
5. atrial fibrillation.mp. (1255)
6. or/1-4 (2289)
7. 5 and 6 (211)

EMBASE (Ovid) 1980 to September 2010

1. (anticoagulant$ or anticoagulation).mp.
2. (anti coagulant$ or anti coagulation).mp.
3. (warfarin or acenocoumarol or coumadin or coumarin or phenprocoumon or sintrom or sinthrome or jantoven or marevan or waran or nicoumalone or dicoumarol or dicumarol).mp.
4. (phenindione or dabigatran or ximelagatran or apixaban or rivaroxaban or edoxaban or azd0837 or ly517717 or ym150 or betrixaban or idraparinux).mp.
5. exp anticoagulant agent/
6. atrial fibrillation.mp.
7. 1 or 2 or 3 or 4 or 5
8. 6 and 7

The Cochrane Library (Cochrane Central Register of Controlled Trials) 2010 Issue 3

1. anticoagulation or anticoagulant*
2. (anti next coagulant*) or (anti next coagulation)
3. MeSH descriptor Anticoagulants explode all trees

4. warfarin or acenocoumarol or coumadin or coumarin or phenprocoumon or sintrom or sinthrome or jantoven or marevan or waran or nicoumalone or dicoumarol or dicumarol
5. phenindione or dabigatran or ximelagatran or apixaban or rivaroxaban or edoxaban or azd0837 or ly517717 or ym150 or betrixaban or idraparinux
6. (1 OR 2 OR 3 OR 4 OR 5)
7. atrial next fibrillation
8. MeSH descriptor Atrial Fibrillation explode all trees
9. (7 OR 8)
10. (6 AND 9)

Appendix 3 Publications not available after contacting authors

Reference	Contact method(s)
Koefoed BG, Gullov AL, Pedersen TS, Petersen P. Dropout and withdrawal from warfarin and aspirin therapy in patients with atrial fibrillation. *Thromb Haemost* 1997;(Suppl.):83–4	E-mail
Lavitola PL, Spina GS, Sampaio RO, Tarasoutchi F, Grinberg M. Bleeding during oral anticoagulant therapy: warning against a greater hazard. *Arq Bras Cardiol* 2009;**93**:174–9	Post, e-mail
Levine MN, Raskob G, Hirsh J. Risk of haemorrhage associated with long term anticoagulant therapy. *Drugs* 1985;**30**:444–60	Post, e-mail
Llobera J, Canameras N, Mas MA, Robles M, Llorach I, Miralles R, *et al*. [Atrial fibrillation and thromboembolic risk in the elderly.] *Rev Multidisciplin Gerontol* 2007; **17**:43–8	Contact details not found
Matsuo S, Nakamura Y, Kinoshita M. Warfarin reduces silent cerebral infarction in elderly patients with atrial fibrillation. *Coron Artery Dis* 1998;**9**:223–6	Post, e-mail
Neutel JM, Smith DHG. A randomised crossover study to compare the efficacy and tolerability of Barr Warfarin sodium to the currently available Coumadin. *Cardiovasc Rev Rep* 1998;**19**:49–59	Post
Ortiz MR, Sanchez MA, Ortega MD, Rubio DM, Del Prado JMA, Zapata MF, *et al*. [Anticoagulation in patients aged less than 75 years with atrial fibrillation.] *Salud Cienc* 2008;**16**:164–7	Post, e-mail

Appendix 4 List of excluded studies

Reasons for exclusion are defined as:

(a) Study design (excluded if study was a commentary or letter, conference abstract published before 2008, case series, studies of bridging therapy with heparin, rationale or study design papers, ecological studies, case–control study).
(b) Population criteria not satisfied (if paper specified the included population with a $CHADS_2$ score of <2, or if the study was conducted primarily on stroke patients with AF whose outcomes were retrieved retrospectively or the population consisted of those with valve replacements or mechanical heart valves).
(c) Intervention criteria not satisfied (if the study did not specify a subgroup of patients on combined ACT plus APT).
(d) Comparator criteria not satisfied (if the paper did not specify a population on ACT alone).
(e) Outcome criteria not satisfied (if none of the desired outcomes were reported and/or outcomes were not reported for both intervention and comparator groups and/or outcomes were retrieved retrospectively in a population of stroke patients with AF).

Reference	Reason(s) for exclusion
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Eikelboom JW, Hirsh J. Combined antiplatelet and anticoagulant therapy: clinical benefits and risks. *J Thromb Haemost* 2007;**5**(Suppl. 1):225–63	a
Gómez FP. Combined anticoagulant/antithrombotic treatment for preventing embolism in atrial fibrillation in geriatrics. *Rev Esp Geriatr Gerontol* 1997;**32**:345–9	a[a]
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Hori M, Koretsune Y. [Multi-centre trial of anti-platelet therapy for the prevention of cerebral infarction in patients with atrial fibrillation: COOPAT (Cooperative Osaka Platelet Antiaggregation Trial) Study.] *Jpn Circ J* 1994;**58**(Suppl. 4):1313–15	a[a]
Janko S, Dorwarth U, Hoffmann E. Pharmacotherapy of atrial fibrillation: an old option with new possibilities. *Exp Opin Pharmacother* 2008;**9**:913–25	a
McBride R. Stroke prevention in atrial fibrillation study. Final results. *Ann Intern Med* 1991;**115**(Suppl. 3):66	a
Parkash R, Wee V, Gardner MJ, Cox JL, Thompson K, Brownell B, *et al*. The impact of warfarin use on clinical outcomes in atrial fibrillation: a population-based study. *Can J Cardiol* 2007;**23**:457–61	a
Preobrazhenskii DV. [Clopidogrel in the treatment of atrial fibrillation: benefit from addition to aspirin. The results of ACTIVE A trial.] *Kardiologiia* 2009;**49**:77	a[a]
Preobrazhenskii DV. [Clopidogrel in the treatment of atrial fibrillation: comparison with warfarin. The results of ACTIVE W trial.] *Kardiologiia* 2009;**49**:78	a[a]
Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, *et al*. Should patient characteristics influence target anticoagulation intensity for stroke prevention in nonvalvular atrial fibrillation?: the ATRIA study. *Circulation* 2009;**2**:297–304	a
Wysokinski WE, McBane RD, Daniels PR, Litin SC, Hodge DO, Dowling NF, *et al*. Periprocedural anticoagulation management of patients with nonvalvular atrial fibrillation. *Mayo Clinic Proceedings* 2008;**83**:639–45. [Erratum published in *Mayo Clin Proc* 2008;**83**:851]	a

Reference	Reason(s) for exclusion
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Handjani AM, Khosropanah S, Habibzadeh F. Safety and antithrombotic effects of fixed low-dose warfarin–aspirin combination in rheumatic mitral stenosis associated with atrial fibrillation. *Iran J Med Sci* 1995;**20**:93–5	b
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Abdelhafiz AH, Myint MP, Tayek JA, Wheeldon NM. Anaemia, hypoalbuminemia, and renal impairment as predictors of bleeding complications in patients receiving anticoagulation therapy for nonvalvular atrial fibrillation: a secondary analysis. *Clin Ther* 2009;**31**:1534–9	c
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Reference	Reason(s) for exclusion
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a Foreign-language papers: reason for exclusion reported is one of the primary reasons agreed by two reviewers.

Appendix 5 Summary of the systematic reviews and meta-analyses included in the review

Author, date	Systematic review/ meta-analysis or both?	Primary objective same as current review? If not, what was primary objective?	Reason for inclusion in current review	Randomised studies included? How many?	Non-randomised studies included? How many?	No. of studies relevant to current review : specify
Anderson 2008[74]	Both	No Efficacy of warfarin in preventing systemic embolism in patients with AF	Systematic review: a few included studies compared effectiveness of ACT vs ACT + APT	Yes 15	No	2 SPAF III[43] AFASAK II[42]
Garwood and Corbett 2008[75]	Systematic review only	No Evaluate data addressing use of anticoagulation in elderly patients with AF, in particular those at risk of falls	Systematic review: a few included studies compared effectiveness of ACT vs ACT + APT	Yes 8	No	2 SPAF III[43] AFASAK II[42]
Hart 2007[20]	Both	No Efficacy and safety of antithrombotic agents for stroke prevention in patients with AF	Systematic review: a few included studies compared effectiveness of ACT vs ACT + APT	Yes 29	No	7 SPAF III[43] AFASAK II[42] FFAACS[41] NASPEAF[39] PETRO[73] SPORTIF III[64] and V[65]
Hughes 2007[76]	Systematic review only	No Risk factors of anticoagulation related bleeding complications in patients with AF	Systematic review: one included study reported bleeding events in patients with AF on ACT + APT	No	Yes 1	1 Shireman 2004[60]
Dentali 2007[77]	Both	No Therapeutic benefits of adding aspirin to ACT in patients receiving ACT therapy	Systematic review: included studies reported events in patients on ACT + APT vs those on ACT alone Only two studies on patients with AF	Yes 10	No	2 AFASAK II[42] FFAACS

Population	Intervention	Comparison	Outcomes	Meta-analysis done? Did meta-analysis include studies relevant to our review?	Comments
Patients with AF/atrial flutter	Warfarin INR ≥2.0	Various: placebo, aspirin, aspirin + clopidogrel, warfarin + aspirin	Systemic embolism, bleeding	Yes SPAF III[43] AFASAK II[42]	Search date: 2007 RCTs only Warfarin effectiveness in preventing systemic embolism/bleeding in non-valvular AF Included SPAF III,[43] AFASAK II[42]
Patients with AF >65 years of age	Warfarin INR target not specified	Warfarin ± aspirin alone, placebo	ICH	No	Search date: 2007 RCTs only Safety (bleeding) of ACT Included SPAF III,[43] AFASAK II[42] Reads like a narrative review No methods section
Patients with non-valvular AF on long-term antithrombotic agents	ACT	Various: placebo, aspirin, aspirin + clopidogrel, warfarin + aspirin	Stroke	Yes AFASAK II[42] NASPEAF	Search date: 2007 RCTs only Stroke prevention in non-valvular AF Included SPAF III,[43] AFASAK II,[42] FFAACS,[41] NASPEAF,[39] PETRO,[73] and SPORTIF III[64] and V[65]
Patients with AF receiving long-term (>4 weeks) ACT	ACT INR ≥2.0	Various: placebo, aspirin, aspirin + clopidogrel, warfarin + aspirin	Patient characteristics of those experiencing a bleeding event on ACT	No	No search date Risk factor identification study. Study selection on basis of occurrence/or not of an event, or presence/absence of a risk factor These are case–control studies Does not aim to compare ACT + APT vs ACT alone
Adult patients receiving ACT No mention of AF, however, the study although identified 2 out of 10 studies with patients on AF	ACT	ACT + aspirin	Arterial TE, mortality, major bleeding	Yes AFASAK II[42] FFAACS	Search date: 2005 RCTs only ACT + APT vs ACT alone in patients with cardiovascular risk (wider population than AF) Include mechanical valves Included AFASAK II,[42] FFAACS – no separate analysis for these

Author, date	Systematic review/ meta-analysis or both?	Primary objective same as current review? If not, what was primary objective?	Reason for inclusion in current review	Randomised studies included? How many?	Non-randomised studies included? How many?	No. of studies relevant to current review : specify
Cooper 2006[78]	Both	No Identify stroke prevention treatments for AF	Systematic review: included studies reported events in patients with AF on ACT + APT vs ACT alone	Yes 20	No	2 SPAF III[43] AFASAK II[42]
Lip and Edwards 2006[79]	Both	No Compared effectiveness of aspirin, warfarin, and ximelagatran as thromboproprophylaxis in patients with non-valvular AF	Systematic review: included studies reported events in patients with AF on ACT + APT vs ACT alone	Yes 13	No	2 SPAF III[43] AFASAK II[42]
Larson and Fisher 2004[80]	Both	No Efficacy and safety of adjusted-dose ACT + aspirin vs adjusted-dose ACT alone	Systematic review: a few included studies in patients with AF compared effectiveness of ACT + APT vs ACT alone Not all studies patients with AF	Yes 9	No	1 FFAACS[41]
Lip 2004[81]	Both	No Effects of preventative ACT and APT in patients with AF with/ without prior stroke or transient ischaemic attack	Review of systematic reviews that included studies comparing ACT + APT vs ACT alone	Yes	No	2 SPAF III[43] AFASAK II[42]
McNamara 2003[82]	Systematic review only	No Efficacy of rate and rhythm control and antithrombotic therapies in patients with AF	Systematic review: patients with AF; a few included studies compared effectiveness of ACT + APT vs ACT alone	Yes 16 (relevant for AF and antithrombotic therapy)	No	2 SPAF III[43] AFASAK II[42]
Perret-Guillaume and Wahl 2003[83]	Systematic review only	No Efficacy of low intensity/mini-/ low-dose ACT for prevention of TE in patients with AF	Systematic review: patients with AF; a few included studies compared effectiveness of ACT + APT vs ACT alone	Yes 4	No	2 SPAF III[43] AFASAK II[42]

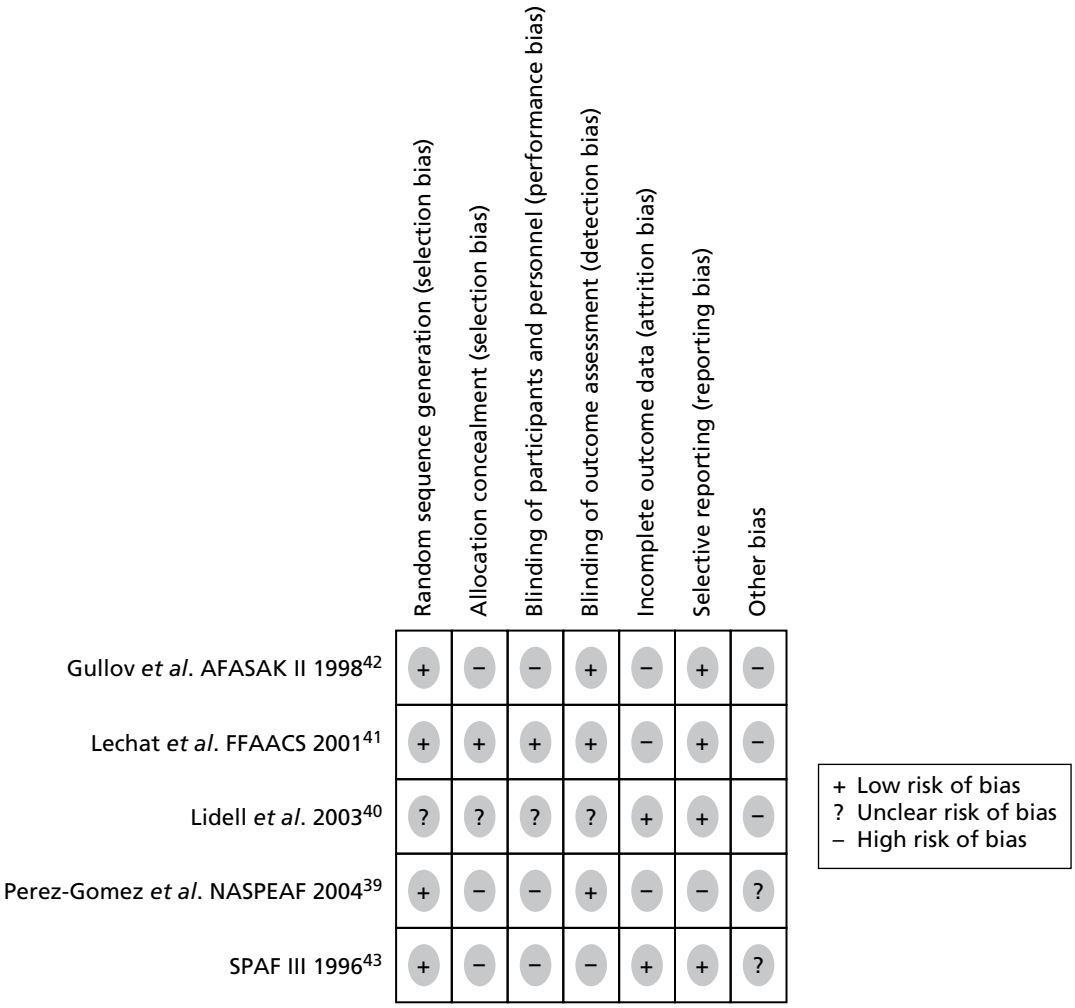
Population	Intervention	Comparison	Outcomes	Meta-analysis done? Did meta-analysis include studies relevant to our review?	Comments
Patients with non-rheumatic AF on long-term antithrombotic therapy	Warfarin	Various: Warfarin, ximelagatran, or aspirin alone Warfarin or ximelagatran + aspirin	Ischaemic stroke, major/minor bleeding	Yes No – mixed-treatment comparison	Search date: 2005 RCTs only Stroke prevention in non-rheumatic AF Included AFASAK II[42] and SPAF III[43] Extensive multiple treatment comparison
Patients with non-valvular AF on ACT + APT vs ACT alone	Warfarin Ximelagatran	Various: Warfarin or ximelagatran alone Warfarin or ximelagatran + aspirin	Ischaemic stroke, mortality, major/minor bleeding	Yes SPAF III[43] AFASAK II[42]	Search date: 2005 RCTs only Stroke prevention in non-valvular AF Included AFASAK II[42] and SPAF III[43] No separate analysis for ACT + APT vs ACT alone
Adult patients receiving ACT + aspirin No mention of AF- the systematic review identified 1 out of 9 studies with patients on AF	Warfarin INR 2.0–3.0	Warfarin (INR 2.0–3.0) + aspirin	TEs, mortality, major/minor bleeding	Yes FFAACS[41] (only one relevant study with patients with AF)	Search date: 2003 RCTs only ACT + aspirin vs ACT only (population wider than just AF) Included FFAACS[41]
Patients with AF with/without prior stroke or transient ischaemic attack on ACT ± APT	Warfarin	Warfarin + aspirin	Stroke, bleeding	No	Search date: 2003 RCTs + systematic reviews Narrative reporting of other evidence sources Included SPAF III[43] and AFASAK II[42]
Adult patients with non-post operative AF	Warfarin	Warfarin + aspirin	Stroke, bleeding	No	Search date: 1998 RCTs only Effectiveness of all therapies Included AFASAK II[42] and SPAF III;[43] poor linking of studies to data
Non-rheumatic patients with AF	Mini-dose, low dose, low-intensity ACT	In two studies, ACT + APT Others, ACT alone	Ischaemic stroke, systemic embolism, all TEs, vascular death	No	Search date: 2002 RCTs only Warfarin dosing in AF Included AFASAK II[42] and SPAF III[43] – limited separate analysis for the studies

Author, date	Systematic review/ meta-analysis or both?	Primary objective same as current review? If not, what was primary objective?	Reason for inclusion in current review	Randomised studies included? How many?	Non-randomised studies included? How many?	No. of studies relevant to current review : specify
Sanchez-Pena and Lechat 2002[84]	Both	No Evaluate efficacy of antithrombotic therapies in high-risk (of TEs) patients with AF	Systematic review: patients with AF; few included studies compared effectiveness of ACT + APT vs ACT alone	Yes 3	No	3 SPAF III[43] AFASAK II[42] FFAACS
Segal 2000[85]	Both	No Summarises evidence regarding prevention of TE in patients with AF	Systematic review: patients with AF; few included studies compared effectiveness of ACT + APT vs ACT alone	Yes 11	No	2 SPAF III[43] AFASAK II[42]
Aronow 1999[86]	Systematic review only	No Review management of older people with AF	Systematic review: patients with AF; a few included studies compared effectiveness of ACT + APT vs ACT alone	Yes	No	2 SPAF III[43] AFASAK II[42]
Ezekowitz and Levine 1999[87]	Systematic review only	No Evaluate evidence supporting use of warfarin and/or aspirin for stroke prevention in patients with AF	Systematic review: patients with AF; a few included studies compared effectiveness of ACT + APT vs ACT alone	Yes 5	No	1 SPAF III[43]
Fera and Giovannini 1999[88]	Systematic review only	No Effect of antithrombotic therapy on stroke risk in patients with AF	Systematic review: patients with AF; few included studies compared effectiveness of ACT + APT vs ACT alone	Yes	No	2 SPAF III[43] AFASAK II[42]
Loewen 1998[89]	Systematic review only	No Efficacy of warfarin + aspirin compared with either agent alone	Systematic review: a few included studies on AF compared effectiveness of AC T + APT vs ACT alone	Yes 5	Yes 11	One RCT SPAF III43
Howard and Duncan 1997[90]	Systematic review only	No Review of trials evaluating warfarin for primary stroke prophylaxis in non-valvular AF to discuss relative benefits and risks of warfarin + aspirin	Systematic review: patients with AF; included studies compared effectiveness of ACT + APT vs ACT alone	Yes 6	No	2 SPAF III[43] AFASAK II[42]

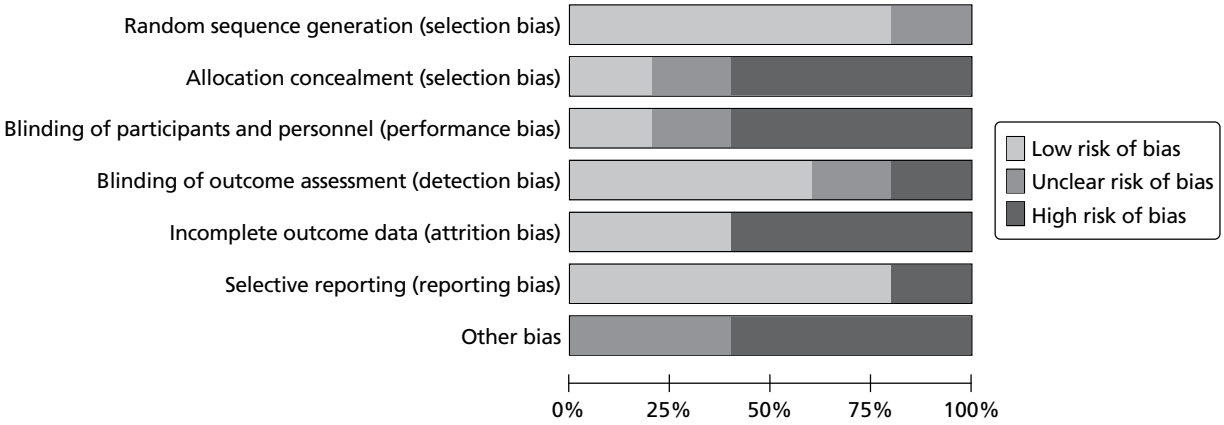
Population	Intervention	Comparison	Outcomes	Meta-analysis done? Did meta-analysis include studies relevant to our review?	Comments
Patients with AF on antithrombotic therapy	ACT alone	Various: ACT alone, APT alone, ACT + APT	Stroke, bleeding	Yes SPAF III43 AFASAK II42 FFAACS	Search date: 2000 RCTs only Included SPAF III,[43] AFASAK II[42] and FFAACS[41]
Studies addressing management of AF	ACT alone	Various: ACT alone, APT alone, ACT + APT	Stroke, major bleeding, deaths	Yes SPAF III,[43] AFASAK II[42]	Search date: 1997 RCTs only Prevention of TE in AF Meta-analysis included SPAF III[43] and AFASAK II[42]
Patients with AF >60 years with any type of management	ACT	ACT + APT	Stroke, systemic TE	No	Search date: 1999 RCTs only Patients with AF Included AFASAK II[42] and SPAF III[43] Study selection unclear
Patients with AF on antithrombotic therapy	ACT alone	Various: Warfarin or aspirin alone, warfarin + aspirin, or placebo	Ischaemic stroke	No	Search date: 1999 RCTs only Prevention of stroke in AF Included SPAF III;[43] limited separate analysis
Patients with AF on antithrombotic therapy	ACT alone	Various: ACT alone, APT alone, ACT + APT	Stroke, systemic TE	No	No search date Unclear if review systematic RCTs only Included SPAF III[43]
Patients on combination warfarin + aspirin or either agent alone	Warfarin	Various: Warfarin or aspirin alone Warfarin + aspirin	TEs, bleeding	No	Search date: 1998 RCTs + non RCTs Warfarin + aspirin in AF Included SPAF III;[43] limited separate analysis
Patients with AF on antithrombotic therapy	Warfarin	Various: Warfarin or aspirin alone Warfarin + aspirin	Stroke, systemic TE	No	Search date: 1997 RCTs only Stroke prevention in non-valvular AF Included SPAF III;[43] limited separate analysis

Appendix 6 Quality assessment of randomised comparisons using the Cochrane Collaboration risk-of-bias tools

Risk-of-bias summary: review of authors' judgements about each risk-of-bias item for each included study



Risk-of-bias graph: review of authors' judgements about each risk-of-bias item, presented as percentages across all included studies



Appendix 7 Studies with data not included in the review and reasons

Author, year	Type of article: primary study/ post hoc or pooled analysis	Aim or objective	Comparison(s)	Outcomes reported	Reason for non-inclusion of data
Randomised comparisons and supporting analyses					
Pérez-Gómez *et al.*, 2006[45]	Subanalysis of NASPEAF[39]	Subanalysis of high-risk group only according to presence or absence of mitral stenosis	Adjusted-dose acenocoumarol (INR 1.4–2.4) + triflusal (600 mg) vs adjusted-dose acenocoumarol (INR 2.0–3.0)	Same as NASPEAF study[39]	Data reported in the NASPEAF paper[39] includes this subpopulation
Pérez-Gómez *et al.*, 2007[44]	Subanalysis of NASPEAF[39]	Subanalysis of according to presence or absence of previous embolism in younger and older population (< 75 years vs > 75 years)	Acenocoumarol (any INR) + triflusal (600 mg) vs adjusted-dose acenocoumarol (INR 2.0–3.0)	Same as NASPEAF study[39]	Data reported in the NASPEAF paper[39] includes this subpopulation
Pérez-Gómez *et al.*, 2007[46]	Review of NASPEAF[39]	Difference in event rates for patients with valvular and non-valvular disease	Acenocoumarol (any INR) + triflusal (600 mg) vs adjusted-dose acenocoumarol (INR 2.0–3.0)	Composite of stroke + TE Bleeding (fatal ICH, GI)	Data reported in the NASPEAF paper[39] includes this subpopulation
Gullov *et al.*, 1999[47]	Primary	Analysis of AFASAK II[42]	Fixed-dose warfarin (1.25 mg) + aspirin (300 mg) vs fixed-dose warfarin (1.25 mg) or adjusted-dose warfarin (INR 2.0–3.0)	Same as AFASAK II study[42]	Duplicate data as the original AFASAK II[42] study
Blackshear *et al.*, 1999[49]	Subanalysis SPAF III[43]	Incidence of TEE and stroke rates according to plaque presence	Adjusted-dose warfarin (INR 1.2–1.5) + aspirin (325 mg) vs adjusted dose warfarin (INR 2.0–3.0)	Death, TE, bleeding (major)	No new data reported
Non-randomised comparisons and supporting analyses					
Lopes *et al.*, 2009 [50]	Primary	Difference in 90-day mortality rates between AF (baseline, new onset and discharge)	Warfarin + aspirin + clopidogrel vs warfarin	Stroke: 90-day rate	Follow-up 90 days Dose of warfarin or APT not specified No. of events not reported for either therapy group (outcomes reported as rate % per patient-year, but no information on patient-year data); no. of participants per therapy group (denominator) not clear
Abdelhafiz and Wheeldon, 2008[51]	Primary	Assess risk factors for bleeding during long-term anticoagulation of AF in older people (> 75 years) in comparison to young people in clinical practice	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin vs adjusted-dose warfarin (INR 2.0–3.0)	Bleeding (major, minor, major + minor)	Only 8 out of 504 patients on combined therapy Follow-up 19 months Dose of aspirin not specified

Author, year	Type of article: primary study/ post hoc or pooled analysis	Aim or objective	Comparison(s)	Outcomes reported	Reason for non-inclusion of data
Amadeus Investigators, 2008[72]	Primary	Idraparinux was non-inferior to VKA for primary outcomes	Idraparinux or VKA + aspirin or ticlopidine/clopidogrel vs idraparinux/VKA	Bleeding (any)	No. of events not reported for combined therapy group Dose of APT not specified; events not reported separately for idraparinux and VKA in combined therapy arms
Suzuki *et al.*, 2007[56]	Primary	Determine incidence and risk factors of major bleeding related to warfarin therapy in Japanese patients	Adjusted-dose warfarin (INR 1.6–2.6) + aspirin vs adjusted-dose warfarin (INR 1.6–2.6)	Bleeding (ICH, major)	Dose of aspirin not specified; no. of events in either therapy group not reported (outcomes reported as rate % per patient-year)
Burton *et al.*, 2006[57]	Primary	Compare events in warfarin-treated patients with AF in primary care, with RCT data	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin vs adjusted-dose warfarin (INR 2.0–3.0)	Bleeding (any)	Dose of aspirin not specified; very small number of participants on combined therapy (n = 18 approx.), no. of patients in either therapy group not clear
Stenestrand *et al.*, 2005[58]	Primary	Probability of receiving an OAC at discharge according to background characteristics and other treatments	OAC + aspirin vs OAC	Death (1-year mortality)	Name of OAC not reported Dose of aspirin not specified Some patients received combined OAC plus aspirin with or without thienopyridine, but numbers (participants) not clear
SPORTIF V investigators, 2005[65]	Primary	Whether or not ximelagatran was non-inferior to warfarin	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (100 mg) vs adjusted-dose warfarin (INR 2.0–3.0) ximelagatran 36 mg (b.i.d.) + aspirin (100 mg) vs ximelagatran 36 mg (b.i.d.)	Bleeding: major + minor	No. of patients on individual therapy (denominator) – unclear Only bleeding outcome reported duplicate in another included study[69]
SPORTIF III Investigators, 2003[64]	Primary	Whether or not ximelagatran was non-inferior to warfarin	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (100 mg) vs adjusted-dose warfarin (INR 2.0–3.0) ximelagatran 36 mg (b.i.d.) + aspirin (100 mg) vs ximelagatran 36 mg (b.i.d.)	Bleeding: major + minor	No. of patients on individual therapy (denominator) – unclear Only bleeding outcome reported duplicate in another included study[69]

Author, year	Type of article: primary study/ post hoc or pooled analysis	Aim or objective	Comparison(s)	Outcomes reported	Reason for non-inclusion of data
White *et al.*, 2007[68]	Pooled analysis SPORTIF III[64] and V[65]	Pooled analysis by anticoagulation (INR) control – only patients on warfarin reported	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (100 mg) vs adjusted-dose warfarin (INR 2.0–3.0)	Bleeding: major Death: all cause Stroke/SE: combined	No. of events not reported for any outcome; event rate % per patient-year reported with no information on either patient-year data or no. of patients (denominator); information on these outcomes also reported in other publication of same studies[69]
Halperin, 2005[71]	Review of SPORTIF III[64] and SPORTIF V[65]	Thromboembolic risk for patients receiving concomitant aspirin therapy in SPORTIF III[64] and V[65] with data on SPORTIF III[64] only	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (100 mg) vs adjusted-dose warfarin (INR 2.0–3.0) ximelagatran 36 mg (b.i.d.) + aspirin (100 mg) vs ximelagatran 36 mg (b.i.d.)	Stroke + SE	Data on patients enrolled in SPORTIF III trial[64] alone, also reported in another included publication[69] reporting pooled data for SPORTIF III and V[64,65]
Douketis *et al.*, 2006[70]	Pooled analysis of SPORTIF III[64] and V[65]	Annual incidence of any (major or minor), major, and intracerebral bleeding with ximelagatran and warfarin therapy during the study period, based on the time to first bleeding episode while patients were treated	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (100 mg) vs adjusted-dose warfarin (INR 2.0–3.0) ximelagatran 36 mg (b.i.d.) + aspirin (100 mg) vs ximelagatran 36 mg (b.i.d.)	Bleeding (major)	No. of events not reported for either therapy group; denominator not reported for combined therapy, outcomes reported as hazard ratios associated with aspirin use
Akins *et al.*, 2007[67]	Pooled analysis of SPORTIF III[64] and SPORTIF V[65]	Comparison of warfarin and ximelagatran for the secondary prevention of stroke	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (100 mg) vs adjusted-dose warfarin (INR 2.0–3.0) ximelagatran 36 mg (b.i.d.) + aspirin (100 mg) vs ximelagatran 36 mg (b.i.d.)	Bleeding, stroke-ischaemic/ haemorrhagic and SE	No. of bleeds reported only for patients with previous embolism Data in another included study[69] envelopes this patient group
Teitelbaum *et al.*, 2008[66]	Pooled analysis of SPORTIF III[64] and SPORTIF V[65]	On-treatment analysis of SPORTIF studies to evaluate if treatment with warfarin vs ximelagatran was had a differential effect on cardioembolic vs non-cardioembolic stroke	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (100 mg) vs adjusted-dose warfarin (INR 2.0–3.0) ximelagatran 36 mg (b.i.d.) + aspirin (100 mg) vs ximelagatran 36 mg (b.i.d.)	Bleeding (primary brain haemorrhage) Stroke (all – clinical types: cardioembolic, non-cardioembolic, uncertain)	No. of patients on individual therapy (denominator) – unclear; stroke outcomes reported in another included study[69]

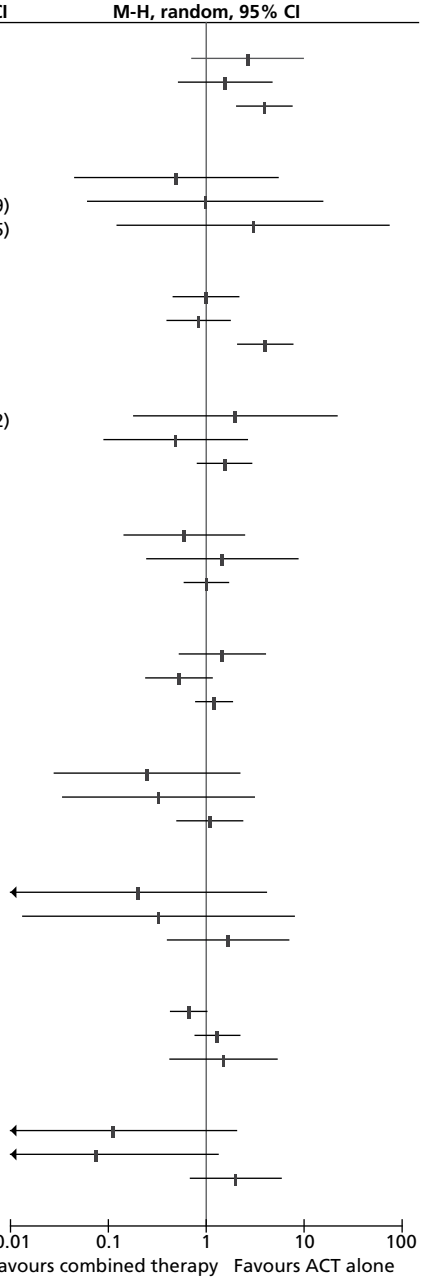
Author, year	Type of article: primary study/ post hoc or pooled analysis	Aim or objective	Comparison(s)	Outcomes reported	Reason for non-inclusion of data
Johnson *et al.*, 2005[59]	Primary	Annual rate of major haemorrhage in previously hospitalised patients on warfarin	Adjusted-dose warfarin (INR 2.0–3.0) + APT vs adjusted-dose warfarin (INR 2.0–3.0)	Bleeding: major	Name of APT not specified; no. of participants not reported for combined therapy group; $n = 228$
Blich and Gross, 2004[61]	Primary	Incidence of thromboembolic and bleeding events in patients with AF	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin (100 mg) vs adjusted-dose warfarin (INR 2.0–3.0)	Bleeding: TE	No. of participants not reported for individual therapy arms, data reported as event rate % per patient-year
Shireman *et al.*, 2004[60]	Primary	Influence of patient-specific factors on concomitant warfarin–antiplatelet therapy and potential impact of combined therapy on bleeding risk	Warfarin + aspirin/clopidogrel/ticlopidine/ dual APT vs warfarin	Bleeding (ICH, major, GI)	Dose of warfarin or APT not specified, outcomes not reported for combination of warfarin with individual APT separately
Klein *et al.*, 2003[62]	Primary	To calculate cumulative major, minor and composite bleeding rates for the 56-day study period	Adjusted-dose warfarin (INR 2.0–3.0)/ heparin + aspirin vs adjusted-dose warfarin (INR 2.0–3.0)	Bleeding (major)	Follow-up 56 days; dose of aspirin not specified; no. of events in combined therapy group not clear; outcomes not reported separately for warfarin + aspirin and heparin + aspirin
Toda *et al.*, 1998[52]	Primary	Relationship between incidence of TE in patients with AF, and (1) underlying disease; (2) type of AF; and (3) antithrombotic therapy	Warfarin + APT vs warfarin	TE	$n = 257$; dose of warfarin or APT not specified; name of APT in combined therapy arm not reported; no. of participants in individual therapy groups not clear
Albers *et al* 1996[53]	Primary	Assess current status of antithrombotic therapy for patients with AF	Adjusted-dose warfarin (INR 2.0–3.0) + aspirin vs adjusted-dose warfarin (INR 2.0–3.0)	Bleeding (per rectum)	$n = 309$, follow-up period not reported; dose of aspirin in combined therapy group not reported; definition of bleeding possibly different in either therapy group

b.i.d., dose administered twice daily; GI, gastrointestinal; OT, on treatment; TEE, transoesophageal echocardiography.

Appendix 8 Forest plots (without summary estimates) for all outcomes by intervention and comparator

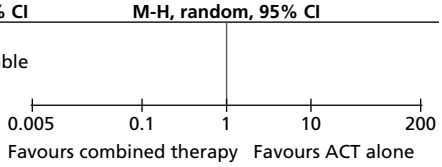
Warfarin plus aspirin compared with warfarin alone

Study or subgroup	Warfarin + aspirin Events	Total	Warfarin alone Events	Total	Risk ratio M-H, random, 95% CI
Stroke (ischaemic)					
AFASAK II[42] (warfarin-adjusted dose)	8	171	3	170	2.65 (0.72 to 9.82)
AFASAK II[42] (warfarin-fixed dose)	8	171	5	167	1.56 (0.52 to 4.68)
SPAF III[43]	43	521	11	523	3.92 (2.05 to 7.52)
SE					
AFASAK II[42] (warfarin-adjusted dose)	1	171	2	170	0.50 (0.05 to 5.43)
AFASAK II[42] (warfarin-fixed dose)	1	171	1	167	0.98 (0.06 to 15.49)
SPAF III[43]	1	521	0	523	3.01 (0.12 to 73.75)
SE					
AFASAK II[42] (warfarin-adjusted dose)	12	171	12	170	0.99 (0.46 to 2.15)
AFASAK II[42] (warfarin-fixed dose)	12	171	14	167	0.84 (0.40 to 1.76)
SPAF III[43]	44	521	11	523	4.02 (2.10 to 7.69)
TIA					
AFASAK II[42] (warfarin-adjusted dose)	2	171	1	170	1.99 (0.18 to 21.72)
AFASAK II[42] (warfarin-fixed dose)	2	171	4	167	0.49 (0.09 to 2.63)
SPAF III[43]	23	521	15	523	1.54 (0.81 to 2.92)
Mortality – vascular					
AFASAK II[42] (warfarin-adjusted dose)	3	171	5	170	0.60 (0.14 to 2.46)
AFASAK II[42] (warfarin-fixed dose)	3	171	2	167	1.46 (0.25 to 8.66)
SPAF III[43]	27	521	27	523	1.00 (0.60 to 1.69)
Mortality – all cause					
AFASAK II[42] (warfarin-adjusted dose)	9	171	6	167	1.46 (0.53 to 4.03)
AFASAK II[42] (warfarin-fixed dose)	9	171	17	170	0.53 (0.24 to 1.15)
SPAF III[43]	42	521	35	523	1.20 (0.78 to 1.86)
Bleeding – major					
AFASAK II[42] (warfarin-adjusted dose)	1	171	4	170	0.25 (0.03 to 2.20)
AFASAK II[42] (warfarin-fixed dose)	1	171	3	167	0.33 (0.03 to 3.10)
SPAF III[43]	13	521	12	523	1.09 (0.50 to 2.36)
Bleeding – ICH					
AFASAK II[42] (warfarin-adjusted dose)	0	171	2	170	0.20 (0.01 to 4.11)
AFASAK II[42] (warfarin-fixed dose)	0	171	1	167	0.33 (0.01 to 7.94)
SPAF III[43]	5	521	3	523	1.67 (0.40 to 6.96)
Bleeding – minor					
AFASAK II[42] (warfarin-adjusted dose)	28	171	42	170	0.66 (0.43 to 1.02)
AFASAK II[42] (warfarin-fixed dose)	28	171	21	167	1.30 (0.77 to 2.20)
SPAF III[43]	6	521	4	523	1.51 (0.43 to 5.30)
ACI					
AFASAK II[42] (warfarin-adjusted dose)	0	171	4	170	0.11 (0.01 to 2.04)
AFASAK II[42] (warfarin-fixed dose)	0	171	6	167	0.08 (0.00 to 1.32)
SPAF III[43]	10	521	5	523	2.01 (0.69 to 5.83)



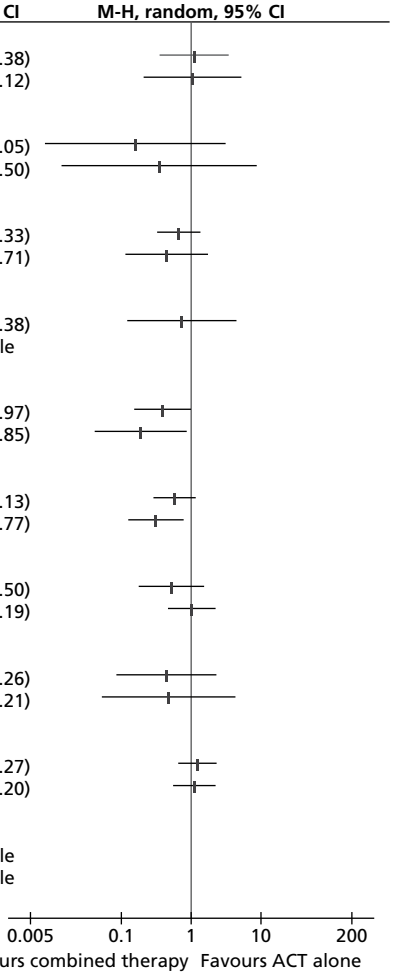
Warfarin plus clopidogrel compared with warfarin alone

Study or subgroup	Warfarin + clopidogrel Events	Total	Warfarin + placebo Events	Total	Risk ratio M-H, random, 95% CI
Bleeding – minor					
Lidell *et al.*[40]	0	0	20	5	Not estimable



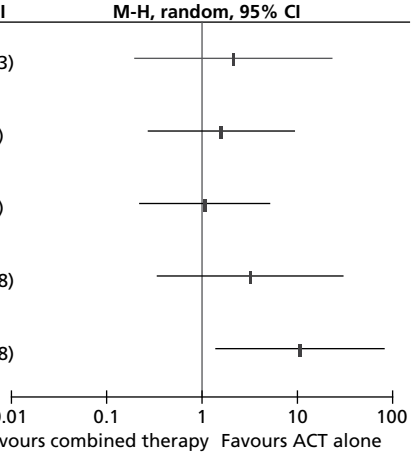
Acenocoumarol plus triflusal compared with acenocoumarol alone

Study or subgroup	Acenocoumarol + triflusal Events	Total	Acenocoumarol alone Events	Total	Risk ratio M-H, random, 95% CI
Stroke (non-fatal)					
NASPEAF[39] (high risk)	6	223	6	247	1.11 (0.36 to 3.38)
NASPEAF[39] (intermediate risk)	3	222	3	232	1.05 (0.21 to 5.12)
SE					
NASPEAF[39] (high risk)	0	223	3	247	0.16 (0.01 to 3.05)
NASPEAF[39] (intermediate risk)	0	222	1	232	0.35 (0.01 to 8.50)
Stroke and SE					
NASPEAF[39] (high risk)	12	223	20	247	0.66 (0.33 to 1.33)
NASPEAF[39] (intermediate risk)	3	222	7	232	0.45 (0.12 to 1.71)
TIA					
NASPEAF[39] (high risk)	2	223	3	247	0.74 (0.12 to 4.38)
NASPEAF[39] (intermediate risk)	0	222	0	232	Not estimable
Mortality – vascular					
NASPEAF[39] (high risk)	6	223	17	247	0.39 (0.16 to 0.97)
NASPEAF[39] (intermediate risk)	2	222	11	232	0.19 (0.04 to 0.85)
Mortality – all cause					
NASPEAF[39] (high risk)	12	223	23	247	0.58 (0.29 to 1.13)
NASPEAF[39] (intermediate risk)	6	222	20	232	0.31 (0.13 to 0.77)
Bleeding – major					
NASPEAF[39] (high risk)	5	222	10	232	0.52 (0.18 to 1.50)
NASPEAF[39] (intermediate risk)	12	223	13	247	1.02 (0.48 to 2.19)
Bleeding – ICH					
NASPEAF[39] (high risk)	2	223	5	247	0.44 (0.09 to 2.26)
NASPEAF[39] (intermediate risk)	1	122	4	232	0.48 (0.05 to 4.21)
Bleeding – minor					
NASPEAF[39] (high risk)	20	223	18	247	1.23 (0.67 to 2.27)
NASPEAF[39] (intermediate risk)	16	222	15	232	1.11 (0.56 to 2.20)
ACI					
NASPEAF[39] (high risk)	0	223	0	247	Not estimable
NASPEAF[39] (intermediate risk)	0	222	0	232	Not estimable



Fluindione plus aspirin compared with fluindione plus placebo

Study or subgroup	Fluindione + aspirin Events	Total	Fluindione + placebo Events	Total	Risk ratio M-H, random, 95% CI
SE					
FFAACS[41]	2	76	1	81	2.13 (0.20 to 23.03)
Mortality – vascular					
FFAACS[41]	3	76	2	81	1.60 (0.27 to 9.31)
Mortality – all cause					
FFAACS[41]	3	76	3	81	1.07 (0.22 to 5.12)
Bleeding – major					
FFAACS[41]	3	76	1	81	3.20 (0.34 to 30.08)
Bleeding – minor					
FFAACS[41]	10	76	1	81	10.66 (1.40 to 81.28)



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