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)

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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