

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

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## Scientific summary

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Health Technology Assessment 2013; Vol. 17: No. 30

DOI: 10.3310/hta17300

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# 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  $\geq 75$  years, heart failure (HF), hypertension and diabetes mellitus, which constitute the recommended and widely used stroke risk assessment tool, the CHADS<sub>2</sub> (Congestive heart failure, Hypertension, Age  $\geq 75$  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<sup>®</sup>, 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

idraparin, and one used dabigatran (Pradaxa<sup>®</sup>, 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<sub>2</sub> [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.

## Publication

Lane DA, Raichand S, Moore D, Connock M, Fry-Smith A, Fitzmaurice DA. Combined anticoagulation and antiplatelet therapy for high-risk patients with atrial fibrillation: a systematic review. *Health Technol Assess* 2013;**17**(30).



# Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Five-year impact factor: 5.804

*Health Technology Assessment* is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

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## This report

The research reported in this issue of the journal was funded by the HTA programme as project number 09/11/02. The contractual start date was in June 2010. The draft report began editorial review in January 2012 and was accepted for publication in September 2012. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

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