Antithrombotic treatment for people with atrial fibrillation and stable coronary artery disease

A large, well conducted Danish observational study analysed the effects of different antithrombotic regimens in people with atrial fibrillation (AF) and stable coronary artery disease. It found that adding antiplatelet therapy (aspirin, clopidogrel or both) to anticoagulant treatment with a vitamin K antagonist (VKA), such as warfarin, was not associated with a reduced risk of recurrent coronary events or of thromboembolism, but was associated with a statistically significant increased risk of bleeding. Regimens based solely on antiplatelet therapy were associated with a higher thromboembolic risk than those that included a VKA; this is consistent with the evidence underpinning the NICE clinical guideline on AF. NICE guidance on secondary prevention of myocardial infarction (MI) recommends that, after 12 months since a person has had an MI, anticoagulation should be continued and the decision on the need for ongoing antiplatelet therapy should take account of the indication for anticoagulation, the person’s thromboembolic, bleeding and cardiovascular risks, and the person’s wishes.

Overview and current advice

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and estimates suggest its prevalence is increasing. If left untreated, AF is a significant risk factor for stroke and other morbidities. Therefore, the aim of treatment is to prevent complications, particularly stroke, and alleviate symptoms. The NICE clinical guideline Atrial fibrillation: the management of atrial fibrillation (CG 180, June 2014) recommends using the CHA₂DS₂-VASc stroke risk score to assess stroke risk in people with symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation; people with atrial flutter; or those with a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm. The HAS-BLED score should be used to assess the risk of bleeding in people who are starting or have started anticoagulation.

The NICE guideline recommends that anticoagulation should be offered to people with AF who have a CHA₂DS₂-VASc score of 2 or above, and considered for men with a CHA₂DS₂-VASc score of 1 taking bleeding risk into account (the CHA₂DS₂-VASc score gives 1 point to all women). Anticoagulation may be with a non-vitamin K anticoagulant (NOAC, that is, apixaban, dabigatran etexilate, rivaroxaban); or a vitamin K antagonist (for example warfarin). The options for anticoagulation should be discussed with the person and the choice should be based on their clinical
features and preferences. NICE has produced a patient decision aid (and associated user guide for healthcare professionals), which may be useful in supporting this shared decision-making.

The AF guideline recommends that aspirin monotherapy should not be offered solely for stroke prevention to people with AF. However, the NICE clinical guideline Myocardial infarction [MI]: secondary prevention (CG 172) recommends that aspirin is offered to all people after an MI and continued indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation. Dual antiplatelet therapy (aspirin plus clopidogrel or ticagrelor) for up to 12 months is recommended in certain circumstances. Having had an MI is itself a risk factor for stroke, so some people who are taking aspirin for secondary prevention after an MI might also be offered anticoagulation. The NICE guideline on secondary prevention after an MI recommends that the person’s bleeding risk, thromboembolic risk and cardiovascular risk should all be taken into account when thinking about treatment if the person has had an MI and also has an indication for anticoagulation. It advises that an antiplatelet drug should be added to anticoagulant treatment in the initial period after an MI in most circumstances, but after 12 months since the MI, anticoagulation should be continued and the decision on the need for ongoing antplatelet therapy should take account of all of the following factors:

- the indication for anticoagulation
- thromboembolic risk
- bleeding risk
- cardiovascular risk
- the person’s wishes.

The guideline recommends against adding a NOAC in combination with dual antiplatelet therapy in people who have had an MI and who otherwise need anticoagulation. It recommends considering using warfarin and discontinuing treatment with a NOAC in such people, unless there is a specific clinical indication to continue it.

See the NICE Evidence topic page on atrial fibrillation and myocardial infarction: secondary prevention for a general overview of these conditions. The NICE Pathways: atrial fibrillation and myocardial infarction: secondary prevention bring together all related NICE guidance and associated products on these conditions in a set of interactive topic-based diagrams.

New evidence

A Danish observational study provides important new evidence because it looked at the benefits and risks of combining antiplatelet drugs and anticoagulants in people with AF and stable coronary artery disease (that is, 12 months after their MI or percutaneous coronary intervention [PCI])

The study was based on a nationwide registry cohort of patients who had AF and had been admitted to hospital for MI or PCI between January 2001 and December 2011. To ensure the study addressed the research question, people who had been admitted to hospital for MI or unstable/stable angina within the following 360 days were excluded. The cohort consisted of 8700 patients with AF and stable coronary artery disease who took various combinations of antithrombotic medication and who were followed up from 2002 until 2011. Their mean age was 74 years and 38% were women. Vitamin K antagonists (VKA, that is, warfarin or phenprocoumon) were taken by 37% of people at inclusion.

Mean follow-up was 3.3 years with a total of 28,947 person-years. The groups that contributed most time at risk were aspirin monotherapy (45%), VKA plus aspirin (26%) and VKA monotherapy (14%). Overall, 89% to 95% of patients had a CHA2DS2-VASc score of 2 or more and 32% to 41% of patients had a HAS-BLED score of 3 or more. The main outcomes were MI/coronary death, fatal/nonfatal thromboembolism (including ischaemic stroke and systemic arterial embolism) and serious bleeding (including intracranial bleeding, gastrointestinal bleeding and anaemia from bleeding), with a
secondary outcome of death from any cause. Results were adjusted for age, sex, inclusion year, MI/PCI status, pharmacotherapy and co-morbidity, including CHA2DS2-VASc and HAS-BLED scores.

Compared with VKA monotherapy, combining VKA with either aspirin or clopidogrel did not statistically significantly affect the risk of MI/coronary death, thromboembolism or death from any cause. However, it did statistically significantly increase the risk of serious bleeding. Combining aspirin plus clopidogrel (dual antiplatelet therapy) with VKA therapy was associated with a statistically significantly increased risk of MI/coronary death, death from any cause, and serious bleeding compared with VKA monotherapy, but no statistically significant difference in thromboembolism. Aspirin or clopidogrel monotherapy or dual antiplatelet therapy were associated with a statistically significantly increased risk of all outcomes compared with VKA monotherapy except for the risk of serious bleeding, which was not statistically significantly different from VKA monotherapy among people taking clopidogrel monotherapy or dual antiplatelet therapy, and statistically significantly reduced among people taking aspirin monotherapy. Adjusted hazard ratios and 95% confidence intervals (CI) compared with VKA monotherapy were:

**MI/coronary death**

- VKA plus aspirin: 1.12, 95% CI 0.94 to 1.34
- VKA plus clopidogrel: 1.53, 95% CI 0.93 to 2.52
- VKA plus dual antiplatelet therapy: 1.76, 95% CI 1.05 to 2.94
- Dual antiplatelet therapy: 2.24, 95% CI 1.76 to 2.84
- Clopidogrel: 1.73, 95% CI 1.27 to 2.34
- Aspirin: 1.73, 95% CI 1.48 to 2.02

**Thromboembolism**

- VKA plus aspirin: 0.86, 95% CI 0.67 to 1.09
- VKA plus clopidogrel: 1.56, 95% CI 0.84 to 2.90
- VKA plus dual antiplatelet therapy: 1.31, 95% CI 0.66 to 2.59
- Dual antiplatelet therapy: 1.77, 95% CI 1.32 to 2.38
- Clopidogrel: 1.73, 95% CI 1.18 to 2.53
- Aspirin: 1.34, 95% CI 1.13 to 1.70

**Serious bleeding**

- VKA plus aspirin: 1.50, 95% CI 1.23 to 1.82
- VKA plus clopidogrel: 1.84, 95% CI 1.11 to 3.06
- VKA plus dual antiplatelet therapy: 2.81, 95% CI 1.82 to 4.33
- Dual antiplatelet therapy: 1.04, 95% CI 0.76 to 1.42
• Clopidogrel: 1.12, 95% CI 0.75 to 1.65
• Aspirin: 0.72, 95% CI 0.59 to 0.87

**Death from any cause**

- VKA plus aspirin: 0.99, 95% CI 0.86 to 1.13
- VKA plus clopidogrel: 1.39, 95% CI 0.94 to 2.06
- VKA plus dual antiplatelet therapy: 1.85, 95% CI 1.29 to 2.65
- Dual antiplatelet therapy: 1.81, 95% CI 1.52 to 2.16
- Clopidogrel: 1.61, 95% CI 1.28 to 2.01
- Aspirin: 1.49, 95% CI 1.32 to 1.67

Observational studies such as this can establish only association, not causation. The authors were not able to adjust for all confounding factors, such as smoking status, use of over-the-counter aspirin and control of anticoagulation, and there was likely to be some residual confounding, particularly by indication. For example, patients at higher risk might have been treated with more intense antithrombotic therapy. In addition, only 15% of the time at risk was contributed by people taking antithrombotic medication regimens other than aspirin monotherapy, VKA monotherapy or VKA plus aspirin, so the results for other regimens are less precise. Nevertheless, the results are broadly consistent with the results of randomised controlled trials, as the authors discuss.

**Commentary**

Commentary provided by Campbell Cowan, Emeritus Consultant Cardiologist, Leeds General Infirmary (Chair of the Guideline Development Group for the NICE clinical guideline on atrial fibrillation, CG 180)

The combination of AF and coronary artery disease is very common. Knowing how to manage patients who have an indication for both anticoagulant and antiplatelet therapy is therefore a common clinical problem.

This observational study (Lamberts et al, 2014)\(^1\) brings useful additional information to bear on this issue. The study considered patients admitted to hospital following MI or for PCI, who remained stable after 12 months. Addition of antiplatelet therapy to VKA monotherapy did not reduce the risk of coronary events, but did increase bleeding risks, suggesting that it is reasonable to consider VKA as monotherapy 12 months after a coronary event.

The study is observational, and subject to confounding bias. However, the results broadly support the recommendations in the NICE clinical guideline on secondary prevention after an MI (CG 172) that, at 12 months post-infarction, anticoagulation should be continued and the need for antiplatelet therapy should be reassessed (see above).

The study also considered risk of thromboembolic problems. In common with other studies, risk was higher for regimens based solely on antiplatelet therapy in comparison with regimens including VKA therapy. This is consistent with the recommendations in the recent NICE clinical guideline on AF (CG 180) that anticoagulation is superior to aspirin for stroke prevention.
Many questions remain – these include the value of combining VKA and antiplatelet drugs in the first year following MI or PCI and the role of antiplatelet therapy in combination with non-vitamin K oral anticoagulants (NOACs); the effects of taking NOACs could not be included in the analysis because of the timeframe of the study. However, the study is useful in offering supportive evidence that for the majority of patients with stable coronary disease and AF, it is reasonable to consider VKA therapy without antiplatelet drugs.

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References


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