Bleeding risk with anticoagulants in atrial fibrillation or venous thromboembolism

A systematic review and meta-analysis found that, compared with warfarin, non-vitamin K antagonist oral anticoagulants were associated with a reduction in fatal bleeding in people with atrial fibrillation or venous thromboembolism.

Overview:
- A systematic review and meta-analysis found that, in people who had atrial fibrillation or venous thromboembolism, non-vitamin K antagonist oral anticoagulants (NOACs) reduced the risk of fatal bleeding by about half compared with warfarin.
- NICE has issued guidance on NOACs for atrial fibrillation and venous thromboembolism.
- Practitioners should be aware of the potential bleeding complications of all anticoagulants and their possible interactions with other drugs.

Background: NOACs are increasingly being used instead of warfarin for treating venous thromboembolism and preventing stroke or systemic embolism in people with non-valvular atrial fibrillation (Chai-Adisaksophia et al. 2015). The 4 NOACs currently licensed in the UK for these indications are apixaban, dabigatran etexilate, edoxaban and rivaroxaban.

Few direct comparisons between different NOACs are available, and key studies have differences in study populations, analyses and other factors. This makes it difficult to choose among NOACs for different indications.

Unlike warfarin, NOACs do not require routine anticoagulant monitoring (NICE 2015). However, bleeding is a common adverse effect of all anticoagulants (MHRA 2013).

Current advice: The NICE pathways on treating venous thromboembolism and atrial fibrillation bring together all related NICE guidance and associated products on these conditions in sets of interactive topic-based diagrams. In both pathways, a vitamin K antagonist (for example, warfarin) and the licensed NOACs are listed as anticoagulant treatment options.
Anticoagulation is standard treatment for venous thromboembolic diseases. In people with atrial fibrillation, the decision to use an anticoagulant should be based on the person’s risk of stroke and bleeding.

The NICE guideline on atrial fibrillation 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.

Anticoagulation with a NOAC or a vitamin K antagonist should be offered to people with atrial fibrillation who have a CHA2DS2-VASc score of 2 or above. Anticoagulation should be 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). The options for anticoagulation should be discussed with the person and the choice based on their clinical features and preferences.

The MHRA has issued advice on contraindications to apixaban, dabigatran etexilate and rivaroxaban. Care should be taken when considering prescribing a NOAC to a person with other conditions, procedures or concomitant treatments that may increase the risk of major bleeding.

The recent NICE Medicines optimisation: key therapeutic topics gives a summary of the NICE technology appraisal guidance on NOACs.

New evidence: A systematic review and meta-analysis of 13 randomised controlled trials (RCTs) by Chai-Adisaksopha et al. (2015) compared bleeding and mortality outcomes among people receiving NOACs or warfarin.

This analysis included studies on NOACs for long-term treatment of venous thromboembolism (8 RCTs) or prevention of secondary stroke or systemic embolism due to non-valvular atrial fibrillation (5 RCTs). It studied 102,843 adults who took warfarin (or heparin/low-molecular-weight heparin, followed by warfarin, titrated to a target international normalised ratio of 2.0 to 3.0) or a NOAC (apixaban [2 RCTs], dabigatran [4 RCTs], edoxaban [2 RCTs] or rivaroxaban [5 RCTs]). Follow-up ranged from 6 to 30 months.

The primary outcomes were the percentage of major bleeding events that were fatal and the incidence of fatal bleeding.

Death from major bleeding was reported in 12 studies. The percentage of major bleeding events that were fatal was higher for people taking warfarin (11.05%, 95% confidence interval [CI] 9.17 to 13.07%) than a NOAC (7.57%, 95% CI 6.53 to 8.68%).

The incidence of fatal bleeding was 0.32 per 100 patient–years (95% CI 0.27 to 0.37) with warfarin and half this (0.16 per 100 patient–years, 95% CI 0.12 to 0.20) with a NOAC. There was a statistically significant reduction in the risk of fatal bleeding with a NOAC compared with warfarin (relative risk=0.53, 95% CI 0.43 to 0.64%, p<0.001).

This study is limited by its inability to identify what proportion of people died from intracranial bleeding or to analyse the results for warfarin according to time spent in the therapeutic range. Just under half of the studies were considered to be at risk of bias, and study duration varied. Study participants were likely to be healthier, younger and more closely monitored than people in clinical practice, and these results may not apply to other indications for anticoagulation.

Commentary by Dr Amitava Banerjee, Senior Clinical Lecturer in Clinical Data Science and Honorary Consultant Cardiologist, University College London:

*Several meta-analyses have already considered NOACs versus warfarin in atrial fibrillation (Dogliotti et al. 2013, Liew et al. 2014) and venous thromboembolism separately (van der Hulle et al. 2014). Another analysis has included data for edoxaban (Hicks et al. 2016), which is the latest of the NOACs to undergo phase 3 trials. There have also been several network meta-analyses and indirect comparisons of NOACs and warfarin (Assiri et al. 2013, Sardar et al. 2013, Dogliotti et
“Studies have suggested that NOACs are similar to warfarin in terms of bleeding outcomes in venous thromboembolism and superior to warfarin for major bleeding in atrial fibrillation. The majority of the difference between NOACs and warfarin is accounted for by reduced rates of intracranial haemorrhage.

“This meta-analysis (Chai-Adisaksopha et al. 2015) combines trial data across atrial fibrillation and venous thromboembolism to assess fatal bleeding and case fatality rate for major bleeding for NOACs and warfarin. It found that fatal bleeding was half as likely with NOACs as warfarin.

“The rationale or clinical relevance of combining data for atrial fibrillation and venous thromboembolism is concerning, because these two patient populations have differing baseline characteristics and different bleeding outcomes in existing meta-analyses (van der Hulle et al. 2014, Hicks et al. 2016).

“The study is limited by the bias of nearly half of the trial data (as noted by the authors), the generalisability of trial populations, and unavailability of information about quality of warfarin control in the comparison arms of the trials. In addition, minor bleeding and non-fatal bleeding outcomes are not considered in this analysis. Included trials lasted for about 6 to 30 months. In practice, the majority of patients will be on lifelong anticoagulants, and we do not know the longer term outcomes.

“Since head-to-head trials of the NOACs are unlikely, observational data will be important in establishing differences between the outcomes of the individual NOACs in ‘real-world’ populations. Further studies in particular subgroups (for example, in people with renal impairment or aged more than 80 years) are necessary to understand the range of complications of NOACs.

“This study does not change clinical practice, where practitioners should prescribe a vitamin K antagonist (for example, warfarin) or a NOAC for people with atrial fibrillation or venous thromboembolism. However, people should be aware of the potential bleeding complications of all anticoagulants and their possible interactions with other drugs. MHRA advice on NOACs, which highlights that haemorrhage is a common adverse effect of all anticoagulants, should continue to be followed.”

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