NICE National Institute for Health and Care Excellence

Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Thromboembolic disease: direct oral anticoagulants compared with warfarin in a real world setting

A UK observational study compared the direct oral anticoagulants (DOACs) apixaban, dabigatran and rivaroxaban with warfarin in people who did and did not have atrial fibrillation. Overall, the study found apixaban to have reduced risk of major bleeding compared with warfarin in both subgroups of patients, which was not seen with dabigatran or rivaroxaban. Both rivaroxaban and apixaban were associated with an increased risk of all-cause mortality compared with warfarin. Health professionals should continue to follow NICE guidance for treating atrial fibrillation, and prophylaxis and treatment of venous thromboembolism.

Overview and current advice

Anticoagulants are used to reduce the risk of stroke and systemic embolism in people with atrial fibrillation (AF), reduce the risk of venous thromboembolism (VTE) and deep vein thrombosis (DVT) in people at increased risk; and treat VTE when it happens and prevent reoccurrence (secondary prevention). Anticoagulants include warfarin and the direct oral anticoagulants (DOACs), also known as non-vitamin K antagonist oral anticoagulants (NOACs). DOACs have been shown in randomised controlled trials (RCTs) to be at least non-inferior to warfarin for efficacy in their licensed indications. Warfarin and DOACs can increase the risk of bleeding, which can be serious or fatal. Existing RCTs have shown different bleeding risks between warfarin and individual DOACs. There are no studies directly comparing DOACs, and the differences in design of individual studies and study populations makes comparison between warfarin and DOACs and among DOACs challenging.

NICE technology appraisal guidance recommends the DOACs apixaban (TA245), dabigatran (TA157) and rivaroxaban (TA170) as options for VTE prophylaxis following elective hip or knee replacement. The recently updated NICE VTE prophylaxis guideline recommends rivaroxaban as the first choice DOAC in this indication, as an equivalent to options involving low molecular weight heparin or aspirin. Apixaban and dabigatran are alternatives if these cannot be used. The NICE guideline does not recommend DOACs or warfarin for VTE prophylaxis in other situations.

The NICE VTE treatment guideline recommends warfarin but not DOACs for treatment and secondary prevention of VTE. However NICE technology appraisals published since the guideline recommend each of the DOACs for treatment and secondary prevention of VTE (apixaban: TA341; dabigatran: TA327; edoxaban: TA354; rivaroxaban: TA261 and TA287). This guideline is currently being updated, and publication is expected in November 2019.

The NICE guidance on AF recommends offering a DOAC or warfarin to people with AF who are at increased risk of stroke, taking their bleeding risk into account, and after a person-centred discussion of the risks and benefits of the different treatment options, including no drug treatment. This guideline is currently being updated, with publication expected in September 2020.

NICE Pathways on atrial fibrillation and VTE bring together all NICE guidance and associated products related to these conditions in interactive topic-based diagrams. The Clinical Knowledge Summaries information on atrial fibrillation, deep vein thrombosis and pulmonary embolism give a general overview of prescribing considerations for these conditions. The NICE medicines optimisation: key therapeutic topic on anticoagulants, including non-vitamin K antagonist oral anticoagulants (NOACs) summarises the evidence-base to support medicines optimisation in these therapeutic areas.

New evidence

A prospective cohort study (Vinogradova Y, et al. 2018) assessed the risk of major bleeding with DOACs and warfarin, and their effectiveness in preventing ischaemic stroke, VTE and all-cause mortality in UK general practice. Two UK primary care databases (Qresearch and Clinical Practice Research Datalink [CPRD]) were used to identify people aged 21 to 99 who were started on warfarin, apixaban, dabigatran or rivaroxaban in the period from January 2011 to October 2016. Edoxaban was not included in the study because it was only licensed in the UK at the end of the study period (2015). Acenocoumarol and phenindione were not included because they are rarely prescribed in the UK. People were excluded if they had a prescription of any anticoagulant in the 12 months before the entry date, had less than 12 months of records before entry, or did not have a valid Townsend score. As the study focused on primary prevention of thromboembolic events, patients with previous VTE were excluded from the risk analysis for VTE. People with previous ischaemic stroke were excluded from the risk analysis of ischaemic stroke.

A total of 196,061 people were included in the study, of whom 103,270 had AF and 92,791 did not. Participants were taking warfarin (132,231 people), apixaban (18,223 people), dabigatran (7,744 people) or rivaroxaban (37,863 people). The mean age of the participants was 75 years (for people with AF) and 66 years (for people without AF).

The primary outcome was major bleeding leading to hospital admission or death. Secondary outcomes were ischaemic stroke or VTE in people without a history of a thromboembolic events or stroke, and all-cause mortality. Adjusted hazard ratios (adjHR) were calculated for each of these taking into account several factors including age, sex, ethnicity, lifestyle factors such as smoking and alcohol consumption, Townsend quintile (a measure of deprivation), body mass index, recent and concurrent use of medicines that may affect the risk of bleeding or interact with anticoagulants (such as non-steroidal anti-inflammatory drugs [NSAIDs], antiplatelets and anticonvulsants) or the risk of thromboembolism (hormone replacement therapy and oral contraceptives), comorbidities, and year of entry into the study. Several sensitivity analyses were also conducted.

Among people with AF, apixaban was associated with a statistically significantly lower risk of major bleeding leading to hospital admission or death than warfarin (adjHR 0.66, 95% confidence interval [CI] 0.54 to 0.79), whereas dabigatran and rivaroxaban did not show a statistically significant difference in risk. More specifically, both dabigatran and apixaban were associated with a statistically significantly reduced risk of intracranial bleeding compared to warfarin (adjHRs 0.45, 95% CI 0.26 to 0.77 and 0.40, 95% CI 0.25 to 0.64, respectively) but the risk with rivaroxaban was not statistically significantly different from warfarin. Compared with warfarin, apixaban was also associated with a statistically significant reduction in risk of major gastrointestinal bleeds (adjHR 0.76, 95% CI 0.58 to 0.99) but dabigatran and rivaroxaban were not. None of the DOACs was associated with a statistically significant difference in risk of ischaemic stoke or VTE compared with warfarin. However apixaban and

rivaroxaban were both associated with a statistically significantly increased risk of all-cause mortality compared with warfarin (adjHR1.13, 95% CI 1.01 to 1.25 and 1.19, 95% CI 1.09 to 1.29, respectively), whereas dabigatran was not. Broadly similar results were seen for apixaban in people who did not have AF.

The authors discuss possible limitations to their study, including the absence of data on non-adherence, surveillance bias (minor bleeds detected in warfarin users at monitoring visits could have been treated before they became major bleeds), the inevitable imperfections of the databases, and the possibility of unknown confounders or confounding by indication (that is, an increased risk due to the condition or the reason the particular anticoagulant was prescribed, rather than the medicine itself).

Commentary

Commentary provided by NICE

This study provides some helpful real world data to compare oral anticoagulant options, which adds to information from randomised controlled trials (RCTs) with their very controlled conditions and very specific entry requirements. The results are broadly in line with the network meta-analysis of RCTs by Sterne et al (2017). Cost-effectiveness and patient preferences also need to be considered (for example, the need for regular monitoring with warfarin might be a major drawback for some people but a significant benefit for others). The authors calculate some numbers needed to treat which help put the hazard ratios calculated by the authors into perspective. Based on these, for every 1000 people with AF who receive apixaban instead of warfarin for 24 months, about 17 would avoid a major bleed, of whom about 7 would avoid an intracranial bleed. For every 1000 people who do not have AF who receive apixaban instead of warfarin for 6 months, about 7 would avoid a major bleed of whom about 3 would avoid a major gastrointestinal bleed. The reported increased risk of all-cause mortality with apixaban and rivaroxaban compared with warfarin is of potential concern but is difficult to explain, and not in keeping with the results seen for the outcomes of major bleeding, ischaemic stroke or VTE. When analysed by dose, a statistically significant difference in favour of warfarin compared with apixaban or rivaroxaban was seen at lower doses but not at higher doses among people with atrial fibrillation. Among people who did not have atrial fibrillation, a statistically significant difference in favour of warfarin compared with all three DOACs was seen at lower doses, but only for warfarin compared with rivaroxaban at higher doses. As all-cause mortality was a secondary outcome in this study, these findings should probably be seen as hypothesis-generating only.

Health professionals should continue to follow NICE guidance for treating atrial fibrillation, and for prophylaxis and treatment of VTE. It is important to support people to choose the treatment option that is most appropriate for their individual values and preferences.

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References

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