Risk of myocardial infarction: oral direct thrombin inhibitors (dabigatran)

A meta-analysis found that oral direct thrombin inhibitors were associated with a statistically significantly increased risk of myocardial infarction compared with warfarin. The absolute risk with dabigatran was a number needed to harm of 188 over 3 to 24 months. The authors of the meta-analysis suggest the increased risk with dabigatran is likely to be due to a class effect of oral direct thrombin inhibitors and not due to a protective effect of warfarin. While this potential risk was factored into the NICE technology appraisal of dabigatran in March 2012, this study adds weight to this potential safety signal. However, the meta-analysis has limitations and further data are needed to investigate this issue further.

Overview and current advice

The new oral anticoagulants currently available in the UK are the direct factor Xa inhibitors, apixaban and rivaroxaban, and the direct thrombin inhibitor, dabigatran etexilate. Dabigatran is licensed and recommended as an option by NICE for the primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip or knee replacement surgery. It is also licensed and recommended as an option by NICE for the prevention of stroke and systemic embolism in people with nonvalvular atrial fibrillation with certain risk factors.

The main trial supporting the use of dabigatran for the prevention of stroke and systemic embolism in people with atrial fibrillation is RE-LY\(^1\). In this noninferiority randomised controlled trial (RCT), dabigatran at 110 mg or 150 mg twice daily was compared with adjusted-dose warfarin in 18,113 people who had atrial fibrillation and a risk of stroke. After a median follow-up of 2 years, dabigatran was at least as effective as warfarin in preventing strokes or systemic embolism with no greater risk of major bleeding. However, RE-LY also found an observed, but not statistically significant increased risk of myocardial infarction (MI) with dabigatran at either dose compared with warfarin, when updated data were used\(^1,2\).
This potential safety concern was considered by the Appraisal Committee for the NICE technology appraisal of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (March 2012). The Committee noted that both doses of dabigatran were associated with an increased risk of acute MI compared with warfarin but in the data considered at that time this was not statistically significant. The Committee heard from the clinical specialists that this reflected a small absolute difference in the incidence of acute MI between the treatment groups, but it was unclear whether this was because of a protective effect of warfarin or a negative effect of dabigatran treatment, and that the effects did not appear to translate into an increased vascular mortality risk.

The Summaries of Product Characteristics for dabigatran state, ‘In the phase III study RE-LY the overall rate of MI was 0.82, 0.81, and 0.64% per year for dabigatran etexilate 110 mg twice daily, dabigatran etexilate 150 mg twice daily and warfarin, respectively, an increase in relative risk for dabigatran of 29% and 27% compared to warfarin. Irrespective of therapy, the highest absolute risk of MI was seen in the following subgroups, with similar relative risk: patients with previous MI, patients 65 years of age or older with either diabetes or coronary artery disease, patients with left ventricular ejection fraction less than 40%, and patients with moderate renal dysfunction. Furthermore a higher risk of MI was seen in patients concomitantly taking aspirin plus clopidogrel or clopidogrel alone.’

See the NICE Evidence topic pages on venous thromboembolism and atrial fibrillation for a general overview of these conditions. The NICE Pathway: venous thromboembolism brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence

The possibility of an increased risk of MI specifically with oral direct thrombin inhibitors compared with warfarin has been considered in a meta-analysis published in September 2013\(^3\). This study investigated whether the increased risk is seen only with dabigatran, whether it is seen with other oral direct thrombin inhibitors, or whether it is a result of a protective effect of warfarin against MI.

The primary meta-analysis included 11 RCTs (n=39,357) that compared oral direct thrombin inhibitors with warfarin for any indication, where the occurrence of MI after randomisation was reported by investigators by any definition. Four RCTs were of dabigatran (n=23,757, the largest being RE-LY [76% of subjects]); 5 were of ximelagatran, which was never launched in the UK (n=14,402); and 2 were of AZD0837, an oral direct thrombin inhibitor in development (n=1198).

Overall, oral direct thrombin inhibitors were associated with a statistically significantly increased risk of MI compared with warfarin (MI was reported in 285 of 23,333 patients treated with oral direct thrombin inhibitors compared with 133 of 16,024 patients treated with warfarin; OR 1.35, 95% CI 1.10 to 1.66, p=0.005 using the fixed-effects model). On subgroup analysis, there was a statistically significantly increased risk of MI with dabigatran compared with warfarin (OR 1.41, 95% CI 1.09 to 1.83, p=0.009 using the fixed-effects model). The authors calculate that the absolute increase in risk was 0.53% over 3 to 24 months (number needed to harm 188).

There was no statistically significantly increased risk of MI with AZD0837 compared with warfarin or with ximelagatran compared with warfarin overall, although there was an increased risk in the 3 trials of ximelagatran for VTE and thromboprophylaxis.
The secondary meta-analysis included 8 RCTs (n=69,615) that compared warfarin with a comparator antithrombotic (aspirin with and without clopidogrel, oral and parenteral factor Xa inhibitors, and oral direct thrombin inhibitors) in the prevention of stroke. There was statistically significant heterogeneity among these trials (p=0.026), therefore a random-effects model was used. Using this model, the overall rate of MI was similar with warfarin or a comparator (403 out of 31,867 with warfarin compared with 503 out of 37,748 with comparator agents; OR 1.06, 95% CI 0.85 to 1.34, p=0.59).

The authors of the study conclude that their findings suggest the increased risk of MI seen with dabigatran in this meta-analysis is likely to be due to a class effect of oral direct thrombin inhibitors and not due to a protective effect of warfarin. However, the study has several important limitations and the findings should be viewed as hypothesis generating only.

Firstly, the data on MI was not a pre-specified endpoint in any of the included trials in the meta-analyses. The definition of MI was pre-specified in less than half of the trials, and not all of the data on MIs were available from the original publications. Secondly, the primary meta-analysis of oral direct thrombin inhibitors compared with warfarin included 11 RCTs, but was heavily weighted by RE-LY, which included the most patients (18,113) for the longest duration of follow-up (2 years).

In addition, heterogeneity between the included trials should be considered. There was no statistically significant heterogeneity (p=0.084) between the included trials in the primary meta-analysis that compared oral direct thrombin inhibitors with warfarin, therefore a fixed-effects model was used. However, the included trials were in very different patient populations (atrial fibrillation, VTE and mechanical heart valves) and included different drugs for different durations of treatment. It is not known whether results based on a random-effects model would also show a statistically significantly increased risk of MI with oral direct thrombin inhibitors. In the secondary meta-analysis, there was statistically significant heterogeneity (p=0.026) between the included trials and a random-effects model was used. However, the meta-analysis compared warfarin with a combined cohort of people taking aspirin alone, aspirin with clopidogrel, oral or parenteral factor Xa inhibitors, or oral direct thrombin inhibitors in different patient populations, and individual studies suggest a protective effect of warfarin could still be a possibility.

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This meta-analysis and an earlier meta-analysis from 2012 raise some important clinical concerns relevant to my day to day practice. There appears to be sufficient data for me to at least factor in the potential increased risk of MI with dabigatran into the decision making process, even taking into account some of the uncertainties with the data. The Summaries of Product Characteristics describe the RE-LY study finding of a higher overall rate of myocardial infarction with dabigatran in comparison to warfarin. Other cautions with the use of dabigatran listed in the Summaries of Product Characteristics include the contraindication in severe renal impairment (creatinine clearance less than 30ml/min), and the potential increased bioavailability (of up to 75%) if the outer capsule is damaged.
The authors of this meta-analysis conclude that the increased risk of MI is likely to be due to a class effect of oral direct thrombin inhibitors. Dabigatran is currently the only oral direct thrombin inhibitor available in the UK. The other new oral anticoagulants, apixaban and rivaroxaban, are direct factor Xa inhibitors and work at a different stage of the coagulation cascade.

Additional data are required to examine if the potential increased risk of MI persists throughout a more prolonged treatment duration. However, this meta-analysis highlights the need for continued vigilance with all medicines that are still relatively new to the market. European regulators are continuing to monitor safety data on dabigatran.

**Study sponsorship**

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**References**