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[Intervention Review]

# Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism

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## ABSTRACT

### Background

Pulmonary embolism is a potentially life-threatening condition in which a clot can travel from the deep veins, most commonly in the leg, up to the lungs. Previously, a pulmonary embolism was treated with the anticoagulants heparin and vitamin K antagonists. Recently, however, two forms of direct oral anticoagulants (DOACs) have been developed: oral direct thrombin inhibitors (DTI) and oral factor Xa inhibitors. The new drugs have characteristics that may be favourable over conventional treatment, including oral administration, a predictable effect, lack of frequent monitoring or re-dosing and few known drug interactions. To date, no Cochrane review has measured the effectiveness and safety of these drugs in the long-term treatment (minimum duration of three months) of pulmonary embolism.

### Objectives

To assess the effectiveness of oral DTIs and oral factor Xa inhibitors for the long-term treatment of pulmonary embolism.

### Search methods

The Cochrane Vascular Trials Search Co-ordinator searched the Specialised Register (last searched January 2015) and the Cochrane Register of Studies (last searched January 2015). Clinical trials databases were also searched for details of ongoing or unpublished studies. We searched the reference lists of relevant articles retrieved by electronic searches for additional citations.

### Selection criteria

We included randomised controlled trials in which patients with a pulmonary embolism confirmed by standard imaging techniques were allocated to receive an oral DTI or an oral factor Xa inhibitor for the long-term (minimum duration three months) treatment of pulmonary embolism.

### Data collection and analysis

Two review authors (LR, JM) independently extracted the data and assessed the risk of bias in the trials. Any disagreements were resolved by discussion with the third author (PK). We used meta-analyses when we considered heterogeneity low. The two primary outcomes were recurrent venous thromboembolism and pulmonary embolism. Other outcomes included all-cause mortality and major bleeding. We calculated all outcomes using an odds ratio (OR) with a 95% confidence interval (CI).

**Main results**

We included five randomised controlled trials with a total of 7897 participants. Two studies tested oral DTIs (dabigatran) and three studies tested oral factor Xa inhibitors (one rivaroxaban, one edoxaban and one apixaban).

Analysis showed no difference in the effectiveness of oral DTIs and standard anticoagulation in preventing recurrent pulmonary embolism (OR 1.02, 95% CI 0.50 to 2.04; two studies; 1602 participants; high quality evidence), recurrent venous thromboembolism (OR 0.93, 95% CI 0.52 to 1.66; two studies; 1602 participants; high quality evidence), deep vein thrombosis (DVT) (OR 0.79, 95% CI 0.29 to 2.13; two studies; 1602 participants; high quality evidence) and major bleeding (OR 0.50, 95% CI 0.15 to 1.68; two studies; 1527 participants; high quality evidence).

For oral factor Xa inhibitors, when we combined the three included studies together in meta-analyses, there was significant heterogeneity for recurrent pulmonary embolism (OR 1.08, 95% CI 0.46 to 2.56; two studies; 4509 participants; $I^2$ = 58%; moderate quality evidence). The oral factor Xa inhibitors were no more or less effective in the prevention of recurrent venous thromboembolism (OR 0.85, 95% CI 0.63 to 1.15; three studies; 6295 participants; high quality evidence), DVT (OR 0.72, 95% CI 0.39 to 1.32; two studies; 4509 participants; high quality evidence), all-cause mortality (OR 1.16, 95% CI 0.79 to 1.70; one study; 4817 participants; moderate quality evidence) or major bleeding (OR 0.97, 95% CI 0.59 to 1.62; two studies; 4507 participants; high quality evidence). None of the studies measured quality of life.

**Authors' conclusions**

There is no evidence of a difference between oral DTIs and standard anticoagulation in the prevention of recurrent pulmonary embolism. Using the GRADE criteria, the quality of evidence was high. The evidence of the effectiveness of oral factor Xa inhibitors for the prevention of recurrent pulmonary embolism was too heterogenous to combine in a pooled analysis. For the outcomes recurrent venous thromboembolism, DVT, all-cause mortality and major bleeding there is no evidence of a difference between DOACs and standard anticoagulation. According to GRADE criteria, the quality of evidence was moderate to high.

## PLAIN LANGUAGE SUMMARY

### Novel oral anticoagulants (DOACs) for the treatment of pulmonary embolism

**Background**

Venous thromboembolism is a condition where a blood clot forms in the deep veins (DVT) (most commonly of the leg) and can travel up to block the arteries in the lungs (pulmonary embolism). Pulmonary embolism is life-threatening and occurs in approximately 3 to 4 per 10,000 people. The chances of getting a pulmonary embolism can increase with risk factors, including previous clots, prolonged periods of immobility (such as travelling on aeroplanes or bed rest), cancer, exposure to oestrogens (pregnancy, oral contraceptives or hormone replacement therapy), blood disorders (thrombophilia) and trauma. A pulmonary embolism is diagnosed by determining the risk factors and scanning the lungs to check for a clot. If a pulmonary embolism is confirmed, patients are treated with an anticoagulant. This prevents further clots from forming. Until recently, the drugs of choice were heparin, fondaparinux and vitamin K antagonists. However, these drugs can cause side effects and have limitations. Recently two classes of direct oral anticoagulants (DOACs) have been developed: direct thrombin inhibitors (DTI) and factor Xa inhibitors. There are particular reasons why oral DTIs and factor Xa inhibitors might be better medicines to use. They can be given orally, they have a predictable effect, they do not require frequent monitoring or re-dosing and they have few known drug interactions. This review measures the effectiveness and safety of these new drugs compared with conventional treatment.

**Key results**

After searching for relevant studies up to January 2015, we found five studies with a combined total of 7897 participants. Studies compared oral direct thrombin inhibitors and factor Xa inhibitors with conventional treatment. We looked at whether treatment for three months prevented further blood clots and pulmonary embolism. The main safety outcomes included mortality and adverse events such as bleeding. This review showed that there was no evidence of a difference between direct thrombin inhibitors and standard treatment in preventing recurrent clots in the lungs or legs. For oral factor Xa inihibitors and the prevention of recurrent clots in the lungs, the studies were too different to form any meaningful conclusion. Furthermore, there was no evidence of a difference in recurrent venous thromboembolism, DVT, mortality or bleeding. No study measured health-related quality of life.

**Quality of the evidence**

For the outcomes recurrent pulmonary embolism and all-cause mortality when comparing oral factor Xa inhibitors and standard anticoagulation we downgraded the quality of the evidence from high to moderate due to the differences in results between the studies and the small number of studies included in this review. The quality of the evidence for all other outcomes was high.