# National Essential Medicine List Medication Review Process
# Adult Hospital Level
# Component: Blood and blood forming organs

**Date:** 19 January 2016

**Medicine:** New oral anticoagulants (NOACs)

**Indication:** Treatment of venous thromboembolism (VTE) and prevention of recurrence.

**Executive summary:**
There are few randomized control trials investigating NOACs for the treatment and prevention of recurrent VTE, compared to standard treatment (low-molecular weight heparin (LMWH) or unfractionated heparin (UFH), followed by a vitamin K antagonist (VKA)). The available trials investigated non-inferiority with the current standard of treatment, and both direct thrombin inhibitors (DTIs) and factor Xa inhibitors showed comparable efficacy outcomes. Safety outcomes (mainly major bleeding) were more favourable towards the NOACs in the studies.

**Introduction:**
Treatment with NOACs may be more favourable, as they have characteristics that are more favourable over heparin and VKAs, such as oral administration, a predictable effect, lack of frequent monitoring and few known drug interactions.[1] This review aims to compare the DTI dabigatran and the factor Xa inhibitor to standard treatment (heparin + VKA).

**PICO: P:** (unlikely) South African population, **I:** NOACs (rivaroxaban and dabigatran), **C:** heparin and warfarin, **O:** treatment of VTE and prevention of recurrence.

**Search strategy:**

1. Cochrane Database:

Three articles, two excluded:

- 1 looked at anticoagulation in pregnancy
- 1 looked at anticoagulation in cancer

2. PubMed:

Search strategy – following terms were used: 'rivaroxaban' OR 'dabigatran', MeSH for venous thromboembolism, versus 'warfarin'.

3. Google Scholar:

Search strategy - 'rivaroxaban' OR 'dabigatran', versus 'warfarin'.

**Selection of studies:**

- Studies were excluded for: costing of treatments, treatment in atrial fibrillation, treatment or prevention in cancer or pregnancy.
- The major studies for rivaroxaban were: EINSTEIN-DVT, pooled analysis of EINSTEIN-DVT and PE, NICE technical appraisal guidance on rivaroxaban for the treatment of DVT and prevention of recurrent DVT and PE.

[1] Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD010956. DOI: 10.1002/14651858.CD010956.pub2.

- The major studies for dabigatran were: RECOVER and RECOVER II.
- The Cochrane study covered both DTIs and factor Xa inhbitors.

**Evidence synthesis:**

## 1. RIVAROXABAN:

### 1.1 EISTEIN-DVT Study[2]

Background

This was a randomized, open-label study comparing the efficacy and safety of rivaroxaban with standard therapy (enoxaparin + VKA) in patients with acute, symptomatic DVT. The treatment group received rivaroxaban 15mg twice daily for the first 3 weeks, followed by 20mg daily for 3, 6, or 12 months. The control group received subcutaneous enoxaparin 1mg per kg twice daily, and VKA (warfarin or acenocoumarol) started with 48 hours after randomization. Enoxaparin was discontinued after INR was 2 or more, and the patient had received at least 5 days enoxaparin. A total of 3449 patients were included in the intention-to-treat primary efficacy endpoint (symptomatic, recurrent venous thromboembolism: composite of DVT and fatal and nonfatal PE), and 3429 were included in the safety analysis (first major or clinically relevant nonmajor bleeding occurring during treatment). (The EINSTEIN: Continued-Treatment study was excluded, as it compared rivaroxaban to placebo.)

Results

- Primary efficacy endpoint - Hazard ratio of 0.68; 95% confidence interval 0.44 to 1.04; P-value < 0.001 for non-inferiority.
- Safety – HR 0.97; 95% CI 0.76 to 1.22; P-value <0.06.

Possible bias

- Study was sponsored by Bayer Schering Pharma and Ortho-McNeil - sponsorship bias
- The trial is open-label, leading to possible bias[3], e.g. internal validity bias, such as patient selection bias, subject retention bias, reporting bias
- Trial was shorter than intended for 5.9% (n=102) rivaroxaban and 5.5% (n=94) standard treatment patients, due to the event-driven style of the trial.

### 1.2 EINSTEIN-DVT, EINSTEIN-PE pooled analysis[4]

Background

This pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE randomized studies investigated the efficacy (primary outcome: symptomatic recurrent VTE – composite of fatal or nonfatal PE or DVT) and safety (clinically relevant bleeding – composite of major and nonmajor clinically relevant bleeding).

Results

Efficacy - HR 0.89; 95% CI 0.66 to 1.19; P-value <0.001 for non-inferiority.
Safety – HR 0.93; 95% CI 0.81 to 1.06; P-value =0.27

[2] The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510
[3] Beyer-Westendorf J, Buller H. External and internal validity of open label or double-blind trials in oral anticoagulation: better, worse or just different? J Thromb Haemost 2011;9:2153-8
[4] Prins *et al* on behalf of the EINSTEIN Investigators. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thrombosis Journal 2013;11:21

Possible bias

The same biases that occurred in the original trials will duplicate here.

### 1.3 Rivaroxaban for the treatment of DVT and prevention of recurrent DVT and PE (NICE technology assessment)[5]

This assessment reviewed the EINSTEIN trial. The Committee concluded that rivaroxaban was as effective as enoxaparin followed by VKA for preventing VTE recurrences. It was noted however that rivaroxaban appeared to be less effective in certain groups of patients, including those for whom 3 months of treatment was clinically indicated. As there was no apparent biological plausibility, and this was based on a small number of events in both groups, there was insufficient evidence to demonstrate that rivaroxaban has substantially different effectiveness across treatment durations. The Committee concluded that the treatment effects of rivaroxaban should be based on the whole trial population of the study.

## 2. DABIGATRAN:

### 2.1 RECOVER Study[6]

Background

This study was a double-blind, double dummy randomized trial. The treatment group received dabigatran 150mg twice daily and the control group received dose-adjusted warfarin, after initial intravenous coagulation. Treatment was administered for 6 months. Primary outcome for efficacy was a comparison between groups of the time to first occurrence of the composite end point of symptomatic VTE in the 6 months after randomization (with intention-to-treat). Safety outcome was measured as a major bleed defined as a fall in haemoglobin level of at least 20g/L. Less severe bleeding was classified as minor.

Results

Efficacy - Hazard ratio 1.10; 95% CI 0.65 to 1.84.

Safety:

- Drop outs:16% (n=204) stopped dabigatran, 126 due to adverse event; 14.5% (n=183) stopped warfarin, 102 due to adverse event.
- Major bleeding occurred 1.6% (20) in dabigatran group, 1.9%(24) in warfarin group; HR 0.82; 95% CI 0.45 to 1.48.
- Major or clinically relevant nonmajor bleeding: HR 0.63; 95% CI 0.47 to 0.84; P=0.002
- Trend to higher incidence of gastrointestinal haemorrhage with dabigatran (4.16%, n=53) than warfarin (2.76%, n=35).

Possible bias

- Boehringer Ingelheim sponsored the study and took part in analyzing the data – sponsorship bias
- Selection bias was noticed by Beyer-Westendorf *et al*[3], who suggested patientswith better compliance were recruited to RECOVER.

### 2.2 RECOVER II Study[7]

[5] Technology appraisal guidance: Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. National Institute for Health and Care Excellence 2012

[6] The RECOVER investigators. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 361;24:2342-52

Background

This trial was conducted on the basis of the low recurrent VTE observed during recruitment to RECOVER, and was of similar study design.

Results

Primary efficacy outcome:

- RECOVER II: HR 1.08; 95% CI 0.64 to 1.80
- Pooled results (RECOVER + RECOVER II): HR 1.09; 95%CI 0.76 to 1.57

Primary safety outcome (major bleed):

- RECOVER II: HR 0.69; 95% CI 0.36 to 1. 32
- Pooled results (RECOVER + RECOVER II): HR 0.73; 95% CI 0.48 to 1.11

## 3. COMBINATION: RIVAROXABAN (factor Xa inhibitors) and DABIGATRAN (DTI)

**3.1 Cochrane Review:** Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Background

This review included 11 randomised controlled trials, of which 2 were dabigatran and 4 rivaroxaban. The reviewers concluded that the quality of evidence was generally high, the results of the studies were consistent and the effect estimates were precise. As such, they indicated that it is unlikely that further studies will change the results presented in this review. Primary outcomes: recurrent VTE and fatal or nonfatal PE. Adverse effects, including major bleeding, was included under secondary outcomes.

Results

**Primary outcomes:** (versus standard coagulation)

| Primary outcomes | Direct thrombin inhibitor | Oral factor Xa |
|---|---|---|
| Reccurent VTE | OR 1.09 (95% CI 0.80 to 1.49) | OR 0.89 (95% CI 0.73 to 1.07) |
| Recurrent DVT | OR 1.08 (95% CI 0.74 to 1.58) | OR 0.75 (95% CI 0.57 to 0.98) |
| Fatal pulmonary embolism | OR 1.00 (95% CI 0.27 to 3.70) | OR 1.20 (95% CI 0.71 to 2.03) |
| Non-fatal pulmonary embolism | OR 1.12 (95% CI 0.66 to 1.90) | OR 0.94 (95% CI 0.68 to 1.28) |
| All-cause mortality | OR 0.84 (95% CI 0.62 to 1.51) | OR 0.84 (95% CI 0.64 to 1.11) |

**Adverse effects:**

- DTIs were associated with fewer major bleeding episodes than standard anticoagulation therapy: OR 0.68 (95% CI 0.47 to 0.98). There was no difference in incidence of adverse effects for dabigatran treatment duration: 3 months versus more than 3 months.

[7] The RECOVER II investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014;129:764-772

- The factor Xa inhibitor group was associated with fewer major bleeding episodes compared with standard anticoagulation therapy (OR 0.57, 95% CI 0.43 to 0.76). There was no difference in incidence in major bleeds between treatment and control groups when treatment was for 3 months, this changed to lower incidence of major bleeds with factor Xa inhitor group compared to standard anticoagulation when treatment was for more than 3 months.

Possible bias

- All studies included in this meta-analysis were sponsored by the pharmaceutical company that formulated the particular drug being tested – sponsorship bias.
- The randomization was not clear for most of the studies – risk of selection bias unclear

**Evidence quality:**
The evidence overall is of good quality, with consistent size effects and small confidence intervals. Of concern, however, is the possibility of sponsorship bias with every study. There was good homogeneity between studies[1].

**Alternative agents:** None.

**Summary:** NOACs are shown to be at least as good as standard therapy of heparin plus VKA in the treatment and prevention of recurrent VTE in a strictly selected group of patients.

Of note is that NOACs have not been tested in a numerous patient populations including pregnancy, adolescents, HIV-infected patients on HAART and those on TB therapy. In the South African setting, these patient groups constitute a significant proportion of patients who would require anticoagulation and any decision should be informed by consideration of their needs.