Assessment of the safety and efficacy of dabigatran etexilate (Pradaxa®) in the primary prevention of venous thromboembolism after major orthopaedic surgery

Results from RE-NOVATE® RE-NOVATE® II RE-MODEL™

EXECUTIVE SUMMARY

- Combined, deep vein thrombosis (DVT) and pulmonary embolism (PE) are estimated to be the third most common cardiovascular disorder after coronary heart disease and stroke[1]
- For patients who undergo major orthopaedic surgery and receive no preventative treatment the risk of experiencing deep vein thrombosis (DVT) is up to 60%[2]
- Results from phase III trials demonstrate dabigatran etexilate (Pradaxa®) has a good efficacy and safety profile for the primary prevention of venous thromboembolism (VTE, the collective term for DVT and PE) after total hip or knee replacement surgery[3-5]
- The Boehringer Ingelheim clinical trials investigating dabigatran etexilate in the primary prevention of VTE are part of the extensive RE-VOLUTION® trial programme which includes eight separate clinical trials investigating the prevention and treatment of venous thromboembolic events

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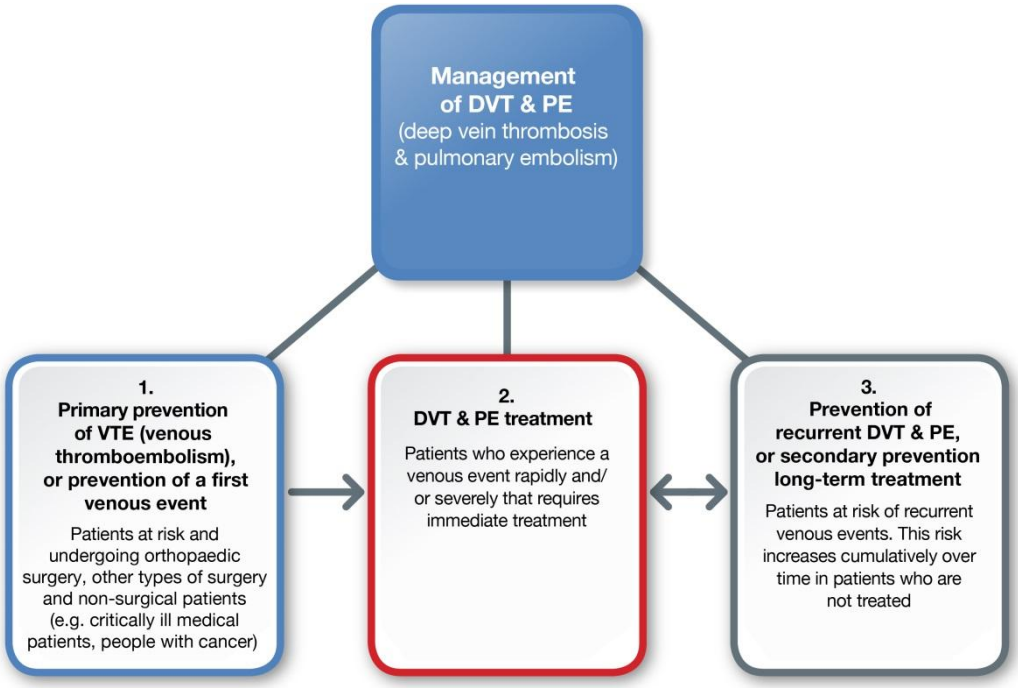
Boehringer Ingelheim

Current management of DVT and PE

The management of DVT and PE takes three main approaches:



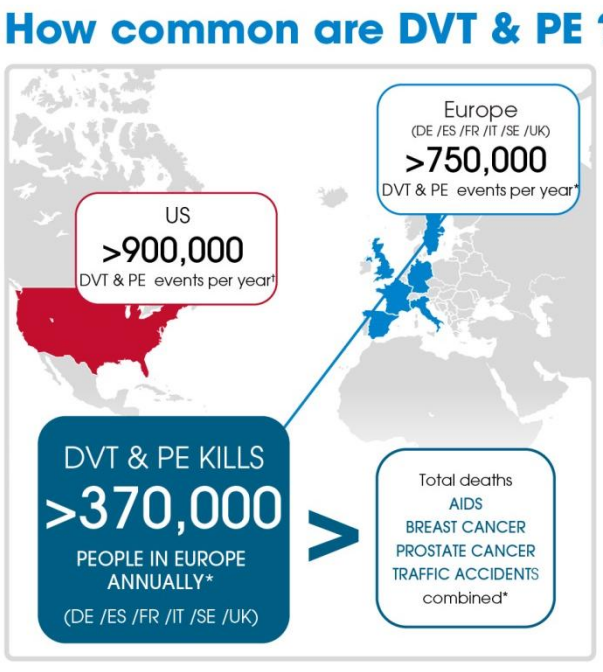
A number of options are currently recommended to treat and provide protection against VTE. The majority of patients are initiated on low molecular weight heparin (LMWH) as the standard of care followed by a dose-adjusted vitamin K antagonist (VKA) which although effective, requires regular blood testing and is associated with drug-drug and food to drug interactions. Novel oral anticoagulants such as dabigatran etexilate, rivaroxaban or apixaban are also recommended.[6,7]

This backgrounder focuses on the results of three phase III clinical trials for dabigatran etexilate for the primary prevention of VTE after major orthopaedic surgery.

Prevention of VTE after major orthopaedic surgery

Primary prevention of VTE focuses on preventing, where possible, a clot from occurring in the first instance.

VTE represents an increasing problem and is estimated to be the third most common cardiovascular disorder after coronary heart disease and stroke.[1] Over 750,000 VTE events are estimated to occur annually in six major EU countries (France, Germany, Italy, Spain, Sweden and UK), and over 900,000 events occur annually in the US.[8,9]



† Roger VL *et al. Circulation.* 2012;**125(1)**:e2-e220.
*Cohen AT, *et al. Thromb Haemost.* 2007;**98**:756–64.

The primary prevention of VTE focuses on people with a known increased risk of developing the condition, such as people undergoing major orthopaedic surgery, especially total hip or knee replacement surgery. PE is considered to be the leading cause of preventable death in hospital.[10]

For patients who undergo major orthopaedic surgery and receive no preventative treatment the risk of experiencing DVT is up to 60%.[2] This is due to the following factors:[11]

- Prolonged immobility and bed rest can lead to blood pooling in the veins, increasing the chance that a clot could form
- Surgery often results in tissue debris, collagen or fats being released into the blood which stimulates blood clotting
- Damage to the walls of the veins during surgery also releases substances which can promote coagulation

It is therefore essential that patients undergoing major orthopaedic surgery receive appropriate preventative treatment to decrease the chance of developing VTE.

Conclusions from phase III trials for prevention of VTE after major orthopaedic surgery

Name of trial	Dose	Conclusions
Dabigatran etexilate for the prevention of VTE after major orthopaedic surgery		
RE-NOVATE®	Dabigatran etexilate 150mg once daily / 220mg once daily *vs.* enoxaparin 40mg once daily	• As effective as enoxaparin for the prevention of VTE in patients after total hip replacement surgery and has a similar safety profile
RE-NOVATE® II	Dabigatran etexilate 220mg once daily *vs.* enoxaparin 40mg once daily	• As effective as enoxaparin for the prevention of VTE in patients after total hip replacement surgery and has a similar safety profile
RE-MODEL™	Dabigatran etexilate 150mg once daily / 220mg once daily *vs.* enoxaparin 40mg once daily	• As effective as enoxaparin for the prevention of VTE in patients after total knee replacement surgery and has a similar safety profile

RE-NOVATE®: Dabigatran etexilate versus enoxaparin for the prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial[3]

Objective: To evaluate the safety and efficacy of two doses of oral dabigatran etexilate (220mg or 150mg once daily) for the prevention of VTE following hip replacement surgery in comparison with enoxaparin 40mg once daily

Study design:

- Randomised, double-blind non-inferiority phase III trial of 3,494 patients scheduled to undergo a total hip replacement at 115 study centres in Europe, Australia and South Africa
- Patients were treated with oral dabigatran etexilate 220mg once daily (n=1,146), oral dabigatran etexilate 150mg once daily (n=1,163) or enoxaparin 40mg subcutaneously once daily (n=1,154) and corresponding placebos
- Treatment was initiated the evening before surgery if enoxaparin / placebo injection and 1-4 hours after surgery with a half-dose if dabigatran etexilate / placebo capsule. Treatment was continued for one month and patients were followed up for three months following surgery

Key findings:

- Dabigatran etexilate was non-inferior to enoxaparin for prevention of VTE in patients undergoing total hip replacement surgery
- The frequency of bleeding was low and comparable between the three groups

Conclusion: Dabigatran etexilate is as effective as enoxaparin for the prevention of VTE in patients after total hip replacement and has a similar safety profile

RE-NOVATE® summary of results:

Primary efficacy & safety outcomes	Dabigatran 220mg once daily	Dabigatran 150mg once daily	Enoxaparin 40mg once daily
Efficacy: VTE events & death *2,651 patients included in efficacy analysis*	**6.0% (53/880)**	**8.6% (75/874)**	**6.7% (60/897)**
Absolute risk difference *vs.* enoxaparin 40mg	-0.7% p=<0.0001	1.9% p=<0.0001	-
Safety: Major bleeding *3,463 patients included in safety analysis*	**2.0% (23/1,146)**	**1.3% (15/1,163)**	**1.6% (18/1,154)**
Clinically relevant non-major bleeding	4.2% (48/1,146)	4.7% (55/1,163)	3.5% (40/1,154)
Minor bleeding	6.1% (70/1,146)	6.2% (72/1,163)	6.4% (74/1,154)

RE-NOVATE® II: Oral dabigatran etexilate versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (replacement)[4]

Objective: To evaluate the efficacy and safety of oral dabigatran etexilate 220mg once daily for prevention of VTE following total hip replacement surgery in comparison with enoxaparin 40mg once daily

Study design:

- Randomised, double-blind, non-inferiority phase III trial of 2,055 patients scheduled to undergo a total hip replacement across 108 sites in 19 countries.
- Patients were treated with either oral dabigatran etexilate 220mg once daily (n=1,010) or enoxaparin 40mg subcutaneously once daily (n=1,003) and corresponding placebos
- Treatment was initiated the evening before surgery if enoxaparin / placebo injection and 1-4 hours after surgery with a half dose if dabigatran etexilate / placebo capsule. Treatment was continued for one month and patients were followed up for three months after surgery

Key findings:

- Dabigatran etexilate was non-inferior to enoxaparin for prevention of VTE in patients undergoing total hip replacement surgery
- A low incidence of major bleeding events was observed with dabigatran etexilate. In the dabigatran etexilate group, over 40% of the major bleeding occurred before administration of active study drug compared to 20% in the enoxaparin patients

Conclusion: Dabigatran etexilate is as effective as enoxaparin for the prevention of VTE after total hip replacement surgery and has a similar safety profile

RE-NOVATE® II summary of results:

Primary efficacy & safety outcomes	Dabigatran 220mg once daily	Enoxaparin 40mg once daily
Efficacy: VTE & death *1,577 patients included in efficacy analysis*	**7.7% (61/792)**	**8.8% (69/785)**
Absolute risk difference *vs.* enoxaparin 40mg	-1.1% p<0.0001	-
Major VTE & death	**2.2% (18/805)**	**4.2% (33/794)**
Absolute risk difference *vs.* enoxaparin 40mg	-1.9% p=0.03	-
Safety: Major bleeding *2,013 patients included in safety analysis*	**1.4% (14/1,010)**	**0.9% (9/1,003)**
Clinically relevant non-major bleeding	2.3% (23/1,010)	2% (20/1,003)
Minor bleeding	6% (61/1,010)	5.4% (54/1,003)

RE-MODEL™: Oral dabigatran etexilate versus subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement[5]

Objective: To evaluate the efficacy and safety of two doses of oral dabigatran etexilate (220mg or 150mg) once daily for the prevention of VTE in patients undergoing total knee replacement in comparison with enoxaparin 40 mg once daily

Study design:

- Randomised, double-blind, non-inferiority phase III trial of 2,101 patients scheduled to undergo a total knee replacement at 105 study centres in 15 countries
- Patients were treated with either oral dabigatran etexilate 220mg once daily (n=679), oral dabigatran etexilate 150mg once daily (n=703) or enoxaparin 40mg subcutaneously once daily (n=694) and corresponding placebos
- Treatment was initiated the evening before surgery if enoxaparin / placebo injection and 1-4 hours after surgery with a half-dose if dabigatran etexilate / placebo capsule. Treatment was continued for 6-10 days following surgery and patients were followed for three months after surgery

Key findings:

- Dabigatran etexilate was non-inferior to enoxaparin for prevention of VTE in patients undergoing total knee replacement
- There was no significant difference in bleeding events between dabigatran etexilate and enoxaparin

Conclusion: Dabigatran etexilate is as effective as enoxaparin for the prevention of VTE after total knee replacement surgery and has a similar safety profile

RE-MODEL™ summary of results:

Primary efficacy & safety outcomes	Dabigatran 220 mg once daily	Dabigatran 150 mg once daily	Enoxaparin 40 mg once daily
Efficacy: VTE & death *1,541 patients included in efficacy analysis*	**36.4% (183/503)**	**40.5% (213/526)**	**37.7% (193/512)**
Absolute risk difference *vs.* enoxaparin 40mg	-1.3% p= 0.0003	2.8% p=0.017	-
Safety: Major bleeding events *2,076 patients included in safety analysis*	**1.5% (10/679)**	**1.3% (9/703)**	**1.3% (9/694)**
Clinically relevant non-major bleeding	5.9% (40/679)	6.8% (48/703)	5.3% (37/694)
Minor bleeding events	8.8% (60/679)	8.4% (59/703)	9.9% (69/694)

Dabigatran etexilate phase III clinical trials at-a-glance

The Boehringer Ingelheim clinical trials investigating dabigatran etexilate in the primary prevention of VTE are part of the extensive RE-VOLUTION® trial programme. The RE-VOLUTION® trial programme includes eight clinical trials investigating the treatment and prevention of venous thromboembolic events:

- Four trials investigating dabigatran etexilate for the prevention of VTE after major orthopaedic surgery
  - RE-NOVATE®
  - RE-NOVATE® II
  - RE-MODEL™
  - RE-MOBILIZE®*
- Two trials investigating dabigatran etexilate in treatment of DVT and PE**
  - RE-COVER™
  - RE-COVER™ II
- Two trials investigating dabigatran etexilate for the prevention of recurrent DVT and PE**
  - RE-MEDY™
  - RE-SONATE™

Results from phase III trials demonstrate dabigatran etexilate has a good efficacy and safety profile across primary prevention, treatment of DVT and PE as well as prevention of recurrent DVT and PE events.[3–5,12–15]

Boehringer Ingelheim and DVT and PE

Boehringer Ingelheim is committed to addressing the need for an effective, safe and convenient treatment option in DVT and PE and has conducted a robust phase III clinical trial programme involving close to 10,000 DVT and PE patients to evaluate the efficacy and safety of dabigatran etexilate.[16]

In 2008, the European Commission granted EU approval for dabigatran etexilate for the primary prevention of VTE in patients who have undergone elective total hip replacement surgery or total knee replacement surgery. Dabigatran etexilate is also approved for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.[17]

In June 2014 dabigatran etexilate was approved by the European Commission for the treatment and prevention of recurrence of DVT and PE.[17] The U.S. Food and Drug Administration (FDA) approved dabigatran etexilate for DVT and PE patients in April 2014.[18]

Across all licensed indications, dabigatran etexilate is approved in over 100 countries worldwide. Clinical experience of dabigatran etexilate equates to over 3 million patient years.[16]

**The RE-MOBILIZE® trial incorporated a more intense and prolonged dosing regimen of enoxaparin, the North American enoxaparin regimen. For more information, please visit, http://clinicaltrials.gov/*

References

1. Goldhaber SZ. Pulmonary embolism thrombolysis: a clarion call for international collaboration. *J Am Coll Cardiol* 1992;**19**:246–247
2. Geerts W. *et al*. Prevention of venous thromboembolism. *CHEST* 2005;**128**(5):3775-3776
3. Eriksson BI. *et al.* Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007;**370**:949–56
4. Eriksson BI. *et al*. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, doubleblind, non-inferiority trial. *Thromb Haemost* 2011;**105**(4):721-9
5. Eriksson BI. *et al*. Oral dabigatran etexilate *vs*. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement:the RE-MODEL randomized trial. *J Thromb Haemost* 2007;**5**:2178–85
6. Falck-Ytter Y. *et al*. Prevention of VTE in Orthopedic Surgery Patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American of Chest Physicians evidence-based clinical practice guidelines. *CHEST* 2012;**141**(2)(suppl): e279S-e325S
7. Guyatt GH. *et al*. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines*. CHEST* 2012;**141**(2_suppl):7S-47S
8. Cohen AT. *et al.* Venous thromboembolism (VTE) in Europe*. Thromb Haemost* 2007;**98**:756–64
9. Roger VL. *et al*. Heart disease and stroke statistics—2012 update: A report from the American Heart Association. *Circulation* 2012;**125(**1):e2-e220
10. BMJ Best Practice. VTE Prophylaxis. Available at: http://bestpractice.bmj.com/best-practice/monograph/1087.html. Last accessed October2014
11. American Academy of Orthopaedic Surgeons. Deep Vein Thrombosis. Available at: http://orthoinfo.aaos.org/topic.cfm?topic=a00219. Last accessed October 2014
12. Ginsberg JS. *et al.* Oral thrombin inhibitor dabigatran etexilate *vs.* North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthoplasty* 2009;**24**(1)1–9
13. Schulman S. *et al.* Dabigatran versus warfarin in the Treatment of Acute Venous Thromboembolism. *N Engl J Med* 2009;**361**:2342–52
14. Schulman S, Kakkar AK, Goldhaber SZ, *et al.* Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation* 2014;**129**:764-772
15. Schulman S. *et al*. Extended Use of Dabigatran, Warfarin or Placebo in Venous Thromboembolism. *N Engl J Med* 2013;**368**:709–18
16. Boehringer Ingelheim data on file
17. Pradaxa® Summary of Product Characteristics. 2014
18. Pradaxa® Prescribing Information. 2014 Available at: http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf Last accessed October 2014