Assessment of the safety and efficacy of dabigatran etexilate (Pradaxa®) in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and the prevention of recurrent DVT and PE

Results from RE-COVER™ RE-COVER™ II RE-MEDY™ RE-SONATE™

Boehringer Ingelheim

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]
- Over 750,000 DVT and PE events are estimated to occur annually in six major EU countries (France, Germany, Italy, Spain, Sweden, UK)[2] and over 900,000 events occur annually in the US[3]
- DVT and PE are serious medical conditions: 30% of PE patients die within three months of developing the conditions, and four out of 10 DVT and PE patients will experience a repeat clot within 10 years of the first[4,5]
- Phase III clinical trial data showed dabigatran etexilate (Pradaxa®) is as effective as warfarin with significantly lower rates of bleeding[6-8]
- The Boehringer Ingelheim clinical trials investigating dabigatran etexilate in the treatment of DVT and PE 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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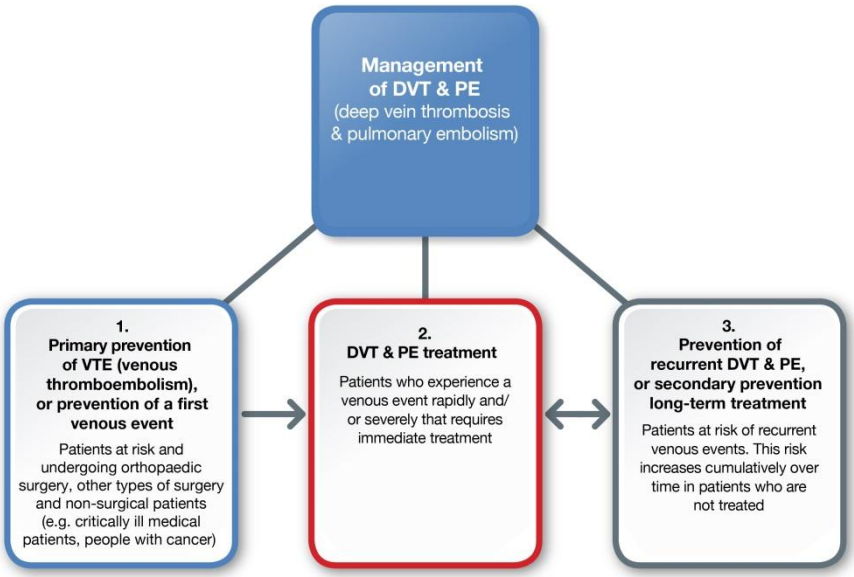
Current management of DVT and PE

The management of DVT and PE takes three main approaches:



There are treatment options for people at every stage of DVT and PE:

1. Protection from an initial clot, known as primary prevention
2. Treating a clot that has already developed
3. Prevention against recurrent clots, known as secondary prevention and long-term treatment

DVT and PE treatment is crucial as 30% of PE patients die within three months.[4]

The main goals when treating blood clots are to: [9]

- Stop a first, or new, clot from forming
- Prevent clots from getting bigger
- Prevent clots from moving to other parts of the body

Specifically for PE, the treatment objective is to prevent death and recurrent clots.[10] 25% of people with either DVT or PE will experience a recurrent clot within five years.[5] The risk of recurrence increases cumulatively for those who do not receive treatment from 11% after one year to 40% after 10 years.[5] It is therefore essential that patients receive secondary prevention treatment to decrease the risk of developing recurrent DVT and PE.

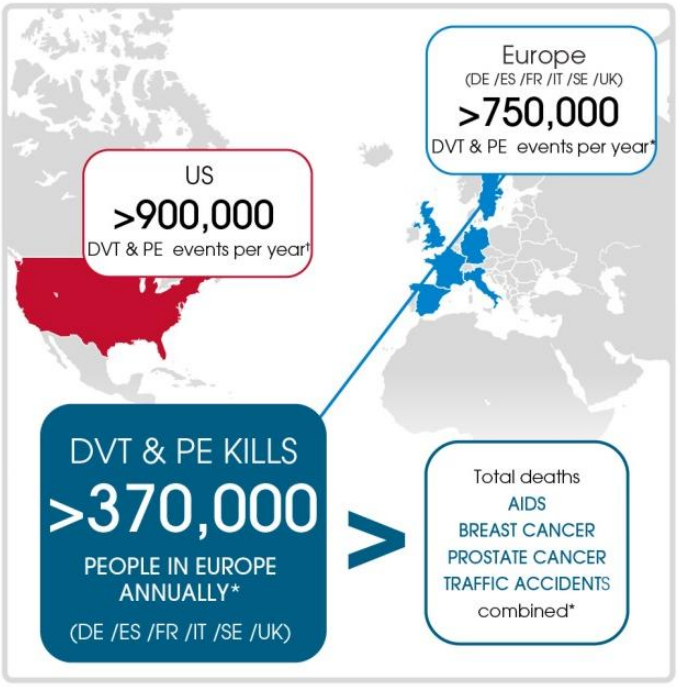
A number of options are currently recommended to treat and provide protection against DVT and PE. The majority of patients are initiated on low molecular weight heparin (LMWH) as the standard of care followed by a dose-adjusted vitamin K antagonist (VKA) which, although effective, requires regular blood testing and is associated with drug-drug and food-to-drug interactions. Novel oral anticoagulants such as dabigatran etexilate, rivaroxaban, apixaban and edoxoban have also been studied in the acute treatment and prevention of recurrent DVT and PE.[6–8, 11–16]

Treatment duration is often between three and six months, but due to the high likelihood of DVT and PE recurrence, long-term anticoagulant treatment beyond three months should be considered in patients who are at risk.[17]

How common are DVT and PE?

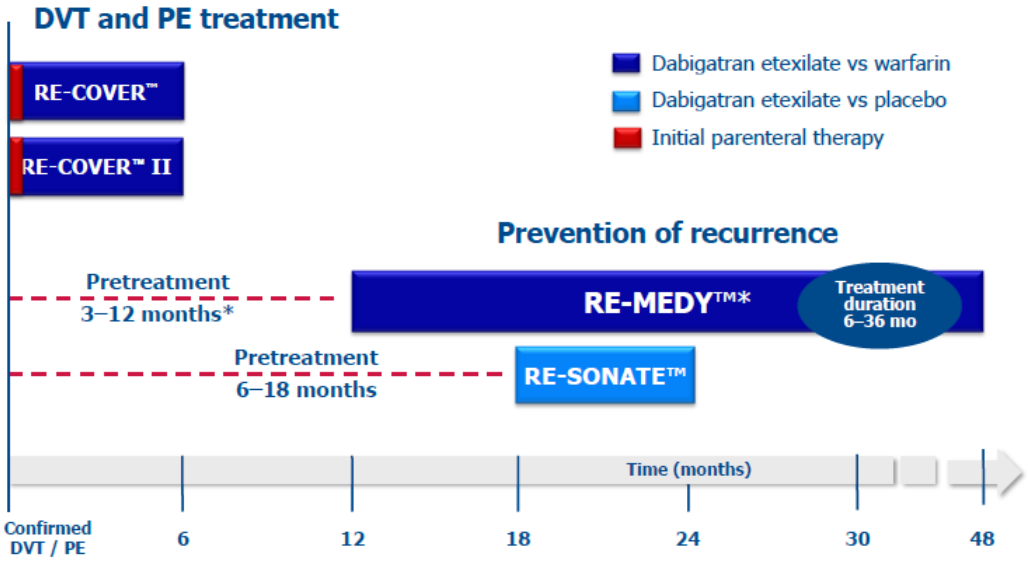
DVT and PE represent an increasing problem and collectively are estimated to be the third most common cardiovascular disorder after coronary heart disease and stroke.[1]

Over 750,000 DVT and PE 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.[2,3]



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

Overview of Boehringer Ingelheim's phase III clinical trials for treatment and prevention of recurrent DVT and PE[7,8]



*RE-MEDY™ original protocol, 3–6 months of pretreatment, then 18 months on study drug; amendment allowed 3–12 months of pretreatment, then up to 36 months on study drug

Name of trial	Dose	Conclusions
Treatment of DVT and PE		
RE-COVER™/ RE-COVER™II (Pooled analysis)	Dabigatran etexilate 150mg twice daily *vs.* warfarin, both following initial heparin treatment	• As effective as warfarin for the treatment of DVT and PE with a significantly lower rate of bleeding**
Prevention of recurrent DVT and PE		
RE-MEDY™	Dabigatran etexilate 150mg twice daily *vs.* warfarin	• As effective as warfarin for the long-term prevention of recurrent DVT and PE, with a significantly lower rate of clinically relevant bleeding
RE-SONATE™	Dabigatran etexilate 150mg twice daily *vs.* placebo	• Significant reduction in risk of recurrent DVT and PE compared to placebo and a low rate of major bleeding

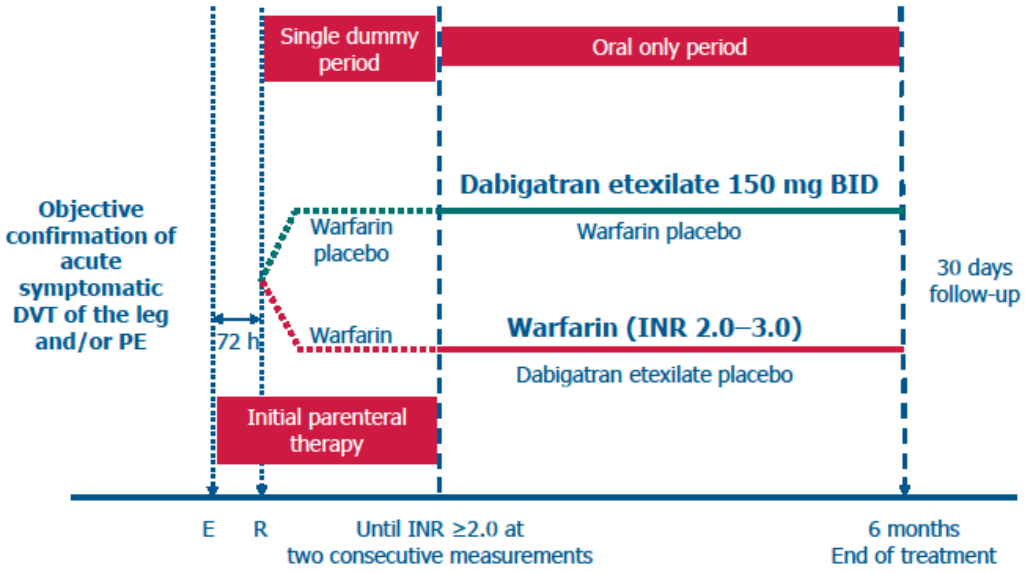
**Safety data from RE-COVER™/RE-COVER™II Pooled Analysis – Scenario 3 (see page 5)

RE-COVER™/RE-COVER™ II: Treatment of Acute Venous Thromboembolism with Dabigatran or Warfarin and Pooled Analysis[7]

Objective: To evaluate the efficacy and safety of oral dabigatran etexilate 150mg twice daily for the treatment of DVT or PE compared with dose-adjusted warfarin, both following initial treatment with heparin.

Study design:

- RE-COVER™ and RE-COVER™ II were duplicate studies and were identical in design
- Together, the two randomised, double-blind, non-inferiority phase III trials included 5,153 patients who had acute symptomatic DVT of the legs or PE
- Patients were all initially treated with an approved injectable anticoagulant (generally unfractioned heparin or low molecular weight heparin) for at least five days. Overlapping warfarin was initiated within 72 hours of starting heparin therapy. When heparin therapy was stopped, patients in the warfarin group continued on warfarin whilst patients receiving the placebo-warfarin received dabigatran etexilate 150mg twice daily
- The duration of treatment was six months. Patients were assessed at seven days and then monthly



Detailed safety analysis:

As part of the analysis of pooled safety data from the combined RE-COVER™ and RE-COVER™ II studies, three scenarios were evaluated:

- **Scenario 1** - From the start of randomisation of any drug. This included bleeding events related to parenteral therapy as well as oral anticoagulant therapy
- **Scenario 2** - From the first intake of study drug (warfarin in single dummy arm, dabigatran etexilate in double dummy arm). This excluded bleeding events associated with parenteral therapy in the dabigatran arm
- **Scenario 3** - Includes oral drugs only (doubly dummy period for dabigatran etexilate and warfarin). This excluded bleeding events associated with parenteral therapy in both arms, and thus compared dabigatran etexilate alone with warfarin alone, and at full pharmacological potential

Scenario 3 is the most relevant scenario to compare the effects of warfarin and dabigatran etexilate as it is the only scenario where both drugs are fully active. The figures shown below refer to this scenario.

Key findings:

- Oral dabigatran etexilate 150mg is as effective as dose-adjusted warfarin for the treatment of DVT and PE
- Dabigatran etexilate showed a significant 40% relative risk reduction in major bleeding and a 44% relative risk reduction in major or clinically relevant bleeding compared to warfarin and a 33% relative risk reduction of total bleeding*

Conclusion: Results from the Pooled Analysis confirm that dabigatran etexilate 150mg twice daily is as effective as warfarin for the treatment of DVT and PE with significantly lower rates of bleeding*

RE-COVER™ & RE-COVER™ II Pooled Analysis summary of results:

Primary efficacy & safety outcomes	Dabigatran 150mg twice daily following initial heparin treatment	Dose-adjusted warfarin following initial heparin treatment
Efficacy: VTE or VTE-related death	**2.7%**	**2.4%**
Safety: Major bleeding	**1.0%**	**1.6%**
Relative risk reduction *vs.* warfarin	40% relative risk reduction	-
Clinically relevant bleeding (including major bleeding)	**4.4%**	**7.7%**
Relative risk reduction *vs.* warfarin	44% relative risk reduction	-
Total bleeding	**14.4%**	**20.4%**
Relative risk reduction *vs.* warfarin	33% relative risk reduction	-

*Safety data from RE-COVER™/RE-COVER™II Pooled Analysis – Scenario 3

RE-MEDY™: Extended Use of Dabigatran or Warfarin in Venous Thromboembolism[8]

Objective: Evaluate the efficacy and safety of 150mg twice daily oral dabigatran etexilate for long-term preventative therapy after an initial DVT or PE, compared to dose-adjusted warfarin.

Study design:

- Randomised, double-blind, non-inferiority phase III trial in 2,856 patients who had previously experienced a symptomatic DVT or PE and considered at increased risk of a recurrent event conducted across 265 sites in 33 countries
- Following 3–12 months of pre-treatment, patients were randomised to receive oral dabigatran etexilate 150mg twice daily or dose-adjusted warfarin. Treatment was continued for up to 36 months. An additional follow-up visit occurred 30 days after the end of treatment
- RE-MEDY™ was the longest of all trials comparing a novel oral anticoagulant to warfarin in this indication

Key findings:

- Oral dabigatran etexilate 150mg is as effective as dose-adjusted warfarin for the extended treatment of DVT and PE
- Results showed a significant 46% relative risk reduction (RRR) for major or clinically relevant bleeding with dabigatran etexilate and a significant 29% RRR in total bleeding events
- Results showed a strong trend towards fewer major bleeding events

Conclusion: Dabigatran etexilate 150mg twice daily is as effective as warfarin for the prevention of recurrent DVT and PE, with significantly lower rates of clinically relevant bleeding

RE-MEDY™ summary of results:

Primary efficacy & safety outcomes	Dabigatran 150mg twice daily	Warfarin
Efficacy: Recurrent VTE & death *2,856 patients included in efficacy analysis*	**1.8% (26/1,430)**	**1.3% (18/1,426)**
Absolute risk difference *vs.* warfarin	0.38% p=0.014	-
Safety: Major bleeding *2,856 patients included in safety analysis*	**0.9% (13/1,430)**	**1.8% (25/1,426)**
Relative risk reduction in major bleeding *vs.* warfarin	48% relative risk reduction p=0.06	-
Major or clinically relevant bleeding	**5.6% (80/1,430)**	**10.2% (145/1,426)**
Relative risk reduction *vs.* warfarin	46% relative risk reduction p<0.001	-
Total bleeding	**19.4% (277/1,430)**	**26.2% (373/1,426)**
Relative risk reduction *vs.* warfarin	29% relative risk reduction p<0.001	-

RE-SONATE™: Extended Use of Dabigatran or Placebo in Venous Thromboembolism[8]

Objective: Evaluate the efficacy and safety of 150mg twice daily oral dabigatran etexilate for long-term preventative therapy after an initial DVT or PE in patients who would not otherwise receive treatment, to determine superiority over placebo.

Study design:

- Randomised, double-blind, phase III trial in 1,343 patients who had previously experienced a symptomatic DVT or PE and considered at risk of a recurrent event across 147 sites in 21 countries
- Following 6-18 months of pre-treatment, patients were randomised to receive oral dabigatran etexilate 150mg twice daily or placebo. Treatment was continued for up to six months. An additional follow-up visit occurred 30 days after the end of treatment and again after 12 months

Key findings:

- Oral dabigatran etexilate 150mg significantly reduced the risk of the recurrent DVT and PE by 92% compared to placebo
- The frequency of major bleeding events was low with dabigatran etexilate. The number of clinically relevant bleeds was higher than placebo, as would be expected when comparing an anticoagulant to no treatment

Conclusion: Dabigatran etexilate 150mg twice daily reduced the risk of recurrent VTE by 92% compared to placebo with a low rate of major bleeding events

RE-SONATE™ summary of results:

Primary efficacy & safety outcomes	Dabigatran 150mg twice daily	Placebo
Efficacy: Recurrent & fatal VTE *1,343 patients included in efficacy analysis*	**0.4% (3/681)**	**5.6% (37/662)**
Relative risk reduction *vs.* placebo	92% p<0.001	-
Safety: Major bleeding *1,343 patients included in safety analysis*	**0.3% (2/684)**	**0% (0/659)**
Clinically relevant bleeding (including major bleeding)	**5.3% (36/684)**	**1.8% (12/659)**

Dabigatran etexilate phase III clinical trials at-a-glance

The Boehringer Ingelheim clinical trials investigating dabigatran etexilate in the treatment of DVT and PE 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 DVT and PE after major 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, DVT and PE treatment as well as prevention of recurrent DVT and PE events.[6–8, 18–21]

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.[22]

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. [23] Dabigatran etexilate is also approved for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.[23]

In June 2014, dabigatran etexilate was approved by the European Commission for the treatment and prevention of recurrence of DVT and PE. [23] The U.S. Food and Drug Administration (FDA) approved dabigatran etexilate for DVT and PE patients in April 2014[24], and approvals have also been achieved in Turkey, Russia, Chile, Argentina, Colombia, Ecuador, Mexico and the Philippines with further registration processes ongoing in other markets.[22]

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.[22]

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