Results from RE-LY® and RELY-ABLE®

Assessment of the safety and efficacy of dabigatran etexilate (Pradaxa®) in long-term stroke prevention

EXECUTIVE SUMMARY

- Dabigatran etexilate (Pradaxa®) has shown a consistent efficacy and safety profile in the prevention of stroke across a wide range of patients with atrial fibrillation (AF)[1-15]

- The RE-LY® trial investigated dabigatran etexilate in the prevention of stroke and systemic embolism in patients with non-valvular AF. It was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) design trial, which compared two fixed doses of the oral direct thrombin inhibitor dabigatran etexilate (110mg and 150mg twice daily) each administered in a blinded manner, with open label warfarin in more than 18,000 patients[1,2 16]

- RE-LY® showed that compared to warfarin (INR 2.0-3.0, TTR 67%[17]), dabigatran etexilate 150mg twice daily provides significant reduction in the risk of both haemorrhagic and ischaemic strokes, while also significantly lowering the risk of life-threatening and intracranial bleeding. Rates of major bleeding were comparable to warfarin[1,2]

- It further showed that dabigatran etexilate 110mg twice daily, indicated for certain patients, was as effective as warfarin for the prevention of stroke and systemic embolism, but with a significantly lower risk for bleeding[1,2]

- Dabigatran etexilate is the first and only novel oral anticoagulant with controlled long-term clinical trial data extending beyond 6 years of ongoing treatment. Results from the RE-LY® follow-up study RELY-ABLE® demonstrate the sustained protection offered by the drug in the clinical setting[14,15]

- Clinical and real world experience of dabigatran etexilate is well established and continues to grow, equating to over 3 million patient-years in all licensed indications in over 100 countries worldwide.[18]

Boehringer Ingelheim

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Study background

Atrial fibrillation (AF) is the most common sustained heart rhythm condition, affecting approximately 2% of the world's population, with one in four adults over 40 developing the condition in their lifetime.[19,20]

AF increases the risk of stroke five-fold.[20] AF-related strokes tend to be severe, with an increased likelihood of death and disability.[21]

Strokes can be classified into two main types: ischaemic and haemorrhagic.[22] Ischaemic strokes account for 92% of strokes experienced by patients with AF.[23]

Vitamin K antagonists, like warfarin, have been used for stroke prevention in AF for over 50 years. However, due to the limitations associated with the treatment, such as the need for regular monitoring and various food-drug and drug-drug interactions which can lead to considerable fluctuations in the treatment's efficacy and safety,[24] patients receiving warfarin spend half of their time outside the recommended narrow therapeutic range.[25] Dabigatran etexilate has been developed to address these limitations.

Investigating dabigatran etexilate for stroke prevention in patients with non-valvular AF

RE-LY®

The RE-LY® (Randomized Evaluation of Long-term anticoagulation therapY) trial was conducted to compare the safety and efficacy of dabigatran etexilate versus warfarin in stroke prevention in patients with atrial fibrillation.[1,2] The positive results of this landmark trial subsequently led to widespread regulatory approval of the treatment for stroke prevention in over 100 countries across the world.

RELY-ABLE®

To ascertain the long-term effects of dabigatran etexilate in stroke prevention and demonstrate the relative benefits of the two doses available, the RELY-ABLE® (Long Term Multi-center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation) study was undertaken. After completion of the 2 year RE-LY® trial, patients taking dabigatran etexilate were followed for a further 2.3 to 4.7 years. The findings demonstrate the long-term protective effects of dabigatran etexilate in the clinical setting, with benefits sustained beyond 6 years of ongoing treatment.[14,15]

The RE-LY® trial

RE-LY® was one of the largest global phase III trials for stroke prevention in AF, enrolling 18,113 patients in 951 centres in 44 countries.[1,2]

The primary objective of RE-LY® was to demonstrate whether dabigatran etexilate was as effective as warfarin in preventing stroke and systemic embolism in patients with non-valvular AF at risk of stroke.[1,2,16]

- Primary endpoint: Incidence of stroke (including haemorrhagic) or systemic embolism
- Secondary measures: All cause death, incidence of stroke (including haemorrhagic strokes), systemic embolism, pulmonary embolism, acute myocardial infarction and vascular death (including death from bleeding)
- Minimum of one year follow-up, maximum of three years and median of two years of follow-up
- In contrast to other studies, RE-LY® involved equal numbers of anticoagulant experienced and naïve patients

RE-LY® trial inclusion criteria

The patient population in RE-LY® were comparably split between stroke risk groups providing a representation of patients encountered in a real-world setting.[5,8,16]

Patients were eligible if they had non-valvular AF documented on electrocardiography performed at screening or within six months beforehand and at least one of the following characteristics: previous stroke or transient ischaemic attack, a left ventricular ejection fraction of less than 40%, New York Heart Association class II or higher, heart-failure symptoms within six months before screening, age of at least 75 years, or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease.[16]

Baseline Characteristics	RE-LY® (N=18,113)
Mean age (years)	71.5
Female (%)	36
$CHADS_2$ score* (%) 0–1 2 ≥3	 31.9 35.6 32.4
Prior stroke, transient ischemic attack or systemic embolism (%)	19.9
Congestive heart failure or left ventricular ejection fraction 40% (%)	32
Vitamin K antagonists (VKA) naïve (%)	50

*$CHADS_2$ risk score: Congestive heart failure, hypertension, age >75 years, diabetes mellitus (1 point each), prior stroke or TIA (count 2 points).

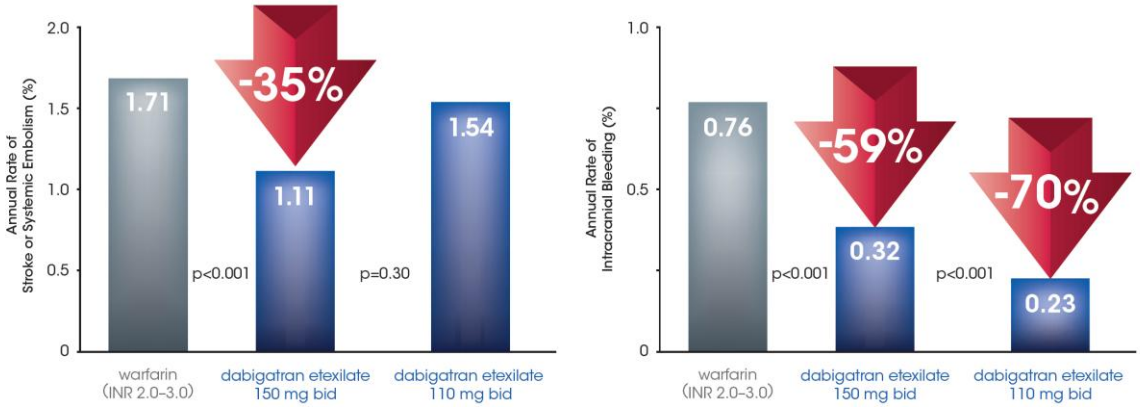
Benefits of a PROBE design[1,16]

The key objective of a phase III trial is to compare a new drug regimen in a large group of patients against the existing standard therapy, to reflect clinical practice as closely as possible. With the use of VKA therapy (warfarin) complicated by the need for continuous monitoring and dose adjustments[24], one of the advantages of undertaking a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) design is that it clearly highlighted the true differences between drug management strategies and demonstrated how dabigatran etexilate performed in daily practice.

The hard clinical endpoints defined in the trial design were unlikely to be affected by subjective judgements from the investigators, and the endpoints were blindly adjudicated by expert physicians. In addition, the two fixed doses of dabigatran etexilate were each administered in a blinded manner.

Key results from the RE-LY® trial

The RE-LY® trial showed that dabigatran etexilate 150mg twice daily was superior to warfarin (INR* 2-3, median TTR** 67%[17]) for stroke prevention in AF.[1,2]



* INR – International Normalized Ratio is a measure of how fast the blood clots

** TTR – Time-in-therapeutic range

bid– twice daily

Dabigatran etexilate 150mg twice daily[1,2]

- Is the only novel oral anticoagulant study of which has shown a significant reduction of both ischaemic and haemorrhagic strokes in patients with non-valvular AF compared to warfarin
- Shows superior stroke prevention compared to warfarin, reducing the risk of stroke and systemic embolism by 35% (Relative Risk Reduction)
- Provides significant reductions in intracranial bleeding (59%) and a reduced risk of total (9%) and life-threatening (20%) bleeding compared to warfarin
- Showed a similar rate of major bleeding as warfarin

Dabigatran etexilate 110mg twice daily[1,2]

- Is as effective as warfarin in reducing the risk of stroke and systemic embolism in patients with AF
- Significantly reduces major (20%), total (22%), life-threatening (33%) and intracranial (70%) bleeding

Tolerability & adverse events

The effectiveness and favourable safety profile of dabigatran etexilate has been well documented both within the RE-LY® trial as well as in further extensive clinical trial programmes, and has passed independent regulatory approval worldwide.[1-15,17] Following in-depth evaluations of the safety and efficacy of Pradaxa®, regulatory authorities including the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) have reconfirmed the favourable benefit-risk profile of the anticoagulant treatment. The findings support the substantial benefits that Pradaxa® offers in real world clinical practice to patients.[26-28]

Dabigatran etexilate 150mg and 110mg twice daily have a similar tolerability and adverse event profile to warfarin. Higher rates of dyspepsia (including abdominal pain and discomfort) were seen with dabigatran etexilate compared to warfarin (11.8% and 11.3% for dabigatran etexilate 150mg twice daily and dabigatran etexilate 110mg twice daily respectively, versus 5.8% for warfarin).[1,2]

In the RE-LY® trial, the subgroup of gastrointestinal bleeding showed an increase with dabigatran etexilate (1.56% for dabigatran etexilate 150mg twice daily compared to 1.08% for warfarin), however, the benefit-risk profile of dabigatran etexilate remains positive.[1,2]

Importantly, treatment with dabigatran etexilate was associated with benefits in terms of reductions in life-threatening bleeding events and in the reduction of intracranial bleeding, one of the most devastating complications of anticoagulant therapy.[1,2,12]

RE-LY® sub-group analyses – Consistency of benefits in a wide range of patients

Sub-group analyses based on data from the RE-LY® trial have shown that dabigatran etexilate is delivering benefits to a wide range of patients with AF.[1-13]

Preventing stroke in patients with AF irrespective of stroke risk[5,8]

- Dabigatran etexilate 150mg twice daily reduced the number of strokes or systemic embolism when compared to warfarin, and 110mg twice daily was comparable to warfarin, irrespective of a patient's risk profile for stroke
- Both doses of dabigatran etexilate were associated with significant reductions in intracranial bleeding compared to warfarin irrespective of a patient's stroke risk profile

Protecting AF patients from recurrent stroke[4]

- Consistent with the overall results from RE-LY®, there were lower numbers of strokes and systemic embolism with dabigatran etexilate 150mg twice daily compared to warfarin in patients with previous transient ischaemic attack or stroke
- Dabigatran etexilate 110mg twice daily was non-inferior to warfarin for the prevention of stroke and systemic embolism with a significant reduction in major haemorrhage in this patient group
- Both doses of dabigatran etexilate provided significant reduction in haemorrhagic strokes and intracranial bleeds

Preventing stroke irrespective of type of AF[3]

- Dabigatran etexilate 150mg twice daily offers improved efficacy compared to warfarin for the prevention of stroke irrespective of the type of AF (paroxysmal, persistent, and permanent)

Providing dose-related benefit irrespective of International Normalized Ratio (INR) control[6]

- Dabigatran etexilate 150mg twice daily was superior to warfarin in the total reduction of stroke and systemic embolism irrespective of centre-based INR control
- Dabigatran etexilate 110mg twice daily was superior to warfarin in the reduction of major bleeding irrespective of centre-based INR control
- Both doses of dabigatran etexilate reduced the rates of intracranial haemorrhage compared to warfarin irrespective of centre-based INR control

Preventing stroke in patients with symptomatic heart failure[9]

- The outcomes in difficult to treat patients with symptomatic heart failure (sHF) were consistent with the results from the main RE-LY® trial
- Dabigatran etexilate 150mg twice daily reduced the risk of stroke, (ischaemic and haemorrhagic), and systemic embolism in AF patients with sHF with similar rates of major bleeding compared to warfarin
- Dabigatran etexilate 110mg twice daily was associated with similar rates of stroke but significantly reduced major bleeding compared to warfarin
- Both doses of dabigatran etexilate significantly reduced intracranial as well as total bleeding in this patient group

Shortening the time of reduced protection against stroke for patients undergoing surgery coupled with similar rates of peri-operative bleeding[10]

- Dabigatran etexilate is associated with a substantially shorter interruption of oral anticoagulation therapy compared to warfarin in patients with AF who require surgery, allowing patients to undergo procedures more quickly and reducing the time of reduced protection against stroke
- Similar rates of bleeding and thrombotic events observed across all treatment groups undergoing surgery or invasive procedures, including those requiring urgent or major surgery
- Lower rates of peri-operative bleeding were observed in patients taking dabigatran etexilate compared to warfarin when surgery was performed within 48 hours of last drug intake

Significantly reducing rates of fatal and traumatic intracranial haemorrhage[12]

- Both dabigatran etexilate 110mg twice daily and 150mg twice daily were associated with significantly fewer fatal intracranial haemorrhage (ICH) events compared to warfarin
- When ICH did occur, the prognosis was similar across all treatments

Demonstrating consistent benefits irrespective of whether patients use concomitant antiplatelet therapy[11]

- Dabigatran etexilate 150mg twice daily maintained its efficacy benefits over warfarin for the prevention of stroke and systemic embolism in AF patients using antiplatelet therapy, with similar rates of major bleeding events
- Dabigatran etexilate 110mg twice daily remained as effective as warfarin with reduction in major bleeding events in this patient group

Providing consistent benefits in both Asian and non-Asian AF patients[13]

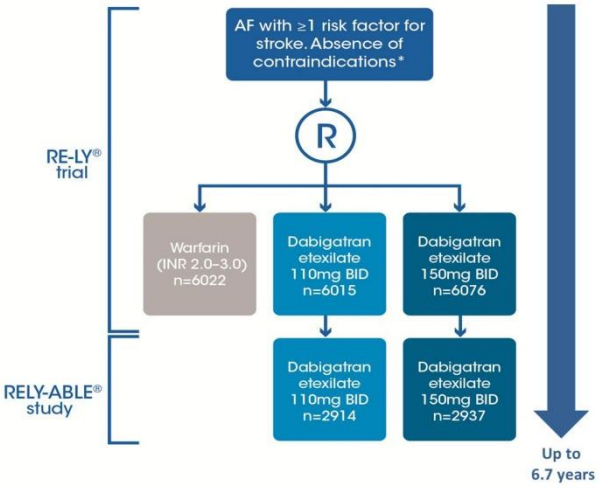
- In line with the overall RE-LY® trial results, dabigatran etexilate 150 mg twice daily reduced the risk of stroke (ischaemic and haemorrhagic) and systemic embolism in Asian patients with AF compared to treatment with warfarin – as it did in non-Asian patients with AF
- Both doses of dabigatran etexilate showed large reductions in the risk of haemorrhagic stroke in Asian AF patients compared to warfarin
- Major bleeding rates as well as total bleeding rates in Asian AF patients were lower with both doses of dabigatran etexilate than warfarin

The RELY-ABLE® study

RELY-ABLE® (Long Term Multi-center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation) was designed to provide additional information on the long-term effects of the two doses of dabigatran etexilate in patients who had completed RE-LY®, providing further insights about the safety and efficacy of the treatment as well as knowledge on the relative benefits of the two doses for stroke prevention in non-valvular AF.[14,15]

RELY-ABLE® patient eligibility & characteristics

In order to determine the long-term effects of dabigatran etexilate, the RELY-ABLE® study involved patients who had completed the RE-LY® trial, were still randomised to receive either dose of dabigatran treatment and were willing to undertake long-term follow-up. Patients continued on the same double-blinded dose of dabigatran etexilate during RELY-ABLE® and the investigated study outcomes matched those defined in RE-LY®.[14,15]



Although the clinical characteristics of patients participating in RELY-ABLE® were generally similar to those who did not, there were some significant differences. Continuing patients were:[14,15]

- More likely to be male
- More likely to have paroxysmal rather than permanent AF
- Less likely to have a history of heart failure

Key results from the RELY-ABLE® study

The unique results from RELY-ABLE® support the benefits of Pradaxa® beyond six years of long-term treatment:[14,15]

- During the additional follow-up period which extended to 4.7 years of treatment beyond RE-LY®, rates of major events for both dabigatran 110 mg and 150 mg twice daily were consistent with those seen in RE-LY®[14,15]
    - Consistent rates of ischaemic and haemorrhagic stroke, and major bleeding with both doses of dabigatran etexilate compared to the event rates that occurred during the RE-LY® trial[14,15]
    - The incidence of haemorrhagic stroke was very low and similar between treatment arms[14,15]
    - Very low rates of intracranial bleeding were sustained through the RELY-ABLE® study[14,15]
- There were no new safety findings identified during the additional observation period of RELY-ABLE®[14,15]

Overall, the combined data from RE-LY® and RELY-ABLE® validate that both doses of dabigatran etexilate are clinically effective for long-term stroke prevention for patients with non-valvular AF, with a favourable safety profile sustained during up to 6.7 years of ongoing treatment.[14,15]

Dabigatran etexilate – Changing treatment for the prevention of stroke in AF

Dabigatran etexilate was the first novel breakthrough oral anticoagulant therapy in over 50 years to be approved for the prevention of stroke and systemic embolism for adult patients with non-valvular AF at risk of stroke. Clinical experience of dabigatran etexilate is already well established and continues to grow, equating to over 3 million patient-years in all licensed indications in over 100 countries worldwide.[18]

Dabigatran etexilate is the only novel oral anticoagulant with over 6 years of controlled clinical data in stroke prevention in AF. The reassuring long-term data demonstrate the sustained efficacy and safety profile of the treatment in the clinical setting.[14,15]

Both the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) have also reaffirmed the important health benefits and safety profile of Pradaxa® for patients with atrial fibrillation when used as directed.[26-28]

The most recent FDA Drug Safety Communication[+] published on 13 May 2014 included results from a Medicare study of more than 134,000 atrial fibrillation patients who were 65 years of age or older and new users of either Pradaxa® or warfarin.[28]

The real-world findings from the Medicare study are consistent with the RE-LY® clinical trial results that provided the basis for the approval of Pradaxa®.[28] The Medicare study demonstrated that in new users, Pradaxa® was associated with a lower risk of clot-related strokes, bleeding in the brain, and death, than warfarin.[28] In line with the known results of the RE-LY® trial, the Medicare study found an increased risk of major GI bleeding in new users of Pradaxa® compared to warfarin.[28] The MI risk was similar for the two drugs.[28]

[+] *In the United States, the licensed doses for dabigatran etexilate are 150mg twice daily and 75mg twice daily for the prevention of stroke and systemic embolism in adult patients with non-valvular AF*[29]. *The dose of 75 mg twice daily is not authorised in Europe for this indication.*[17]

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